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CORONARY ARTERIOSCLEROSIS AND MYOCARDIAL HYPERTROPHY*

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CARDIAC hypertrophy commonly occurs with disturbances that increase the work of the heart. These include valvular defects, intracardiac or other vascular shunts and hypertension of either the pulmonary or the systematic circuits. In these situations the cause is apparent and the result follows naturally. The heart is subjected to unusual or excessive work, and it follows that the myocardium enlarges in a manner analogous to the development of increased muscle mass in weight lifters and wrestlers.

Other conditions with myocardial hypertrophy exist, however, in which the cause is either less clear or totally obscure. Myocarditis may result in myocardial hypertrophy, and, rarely, extensive enlargement of the heart muscle is seen without demonstrable cause. Finally, hypertrophy of the heart is a common finding in patients with coronary disease, a condition in which the blood supply of the heart is actually *less* than adequate. Coronary insufficiency as a cause of myocardial hypertrophy has been noted in the past by various observers. However, for reasons that are not immediately clear, this concept has not been commonly accepted. A pathological diagnosis of hypertensive heart disease is frequently made when hypertrophy is found at autopsy, despite the total absence of known hypertension during life.

This report represents an attempt to clarify the role of coronary arteriosclerosis in the production of cardiac hypertrophy and to indicate the incidence of cardiomegaly in association with coronary disease.

TABLE 1. *Cases of Coronary Arteriosclerosis Without Hypertension.*

CASE NO.	AGE	BODY WEIGHT	CARDIAC WEIGHT	CARDIAC-WEIGHT: BODY-WEIGHT RATIO
	yr.	lb.	gm.	%
1	73	160	465	0.64
2	46	167	425	0.56
3	70	145	420	0.64
4	39	130	425	0.72
5	49	180	610	0.75
6	72	130	480	0.81
7	61	136	660	1.07
8	55	130	460	0.78
9	60	150	480	0.70
10	66	160	425	0.58
11	57	160	460	0.63
12	48	159	445	0.62
13	58	140	430	0.68
14	48	170	520	0.67
15	50	225	625	0.61
16	52	190	500	0.58
17	44	200	605	0.67
18	52	164	425	0.57
19	53	171	515	0.66
20	57	165	520	0.69
21	61	160	460	0.63
22	52	170	545	0.71
23	57	135	400	0.65
24	58	140	365	0.54
25	65	140	370	0.58
26	38	185	400	0.48
27	59	160	340	0.47
28	75	128	330	0.57
29	71	130	325	0.55
30	47	110	280	0.56

TABLE 2. *Cases of Coronary Arteriosclerosis with Hypertension.*

CASE NO.	AGE	BODY WEIGHT	CARDIAC WEIGHT	CARDIAC-WEIGHT: BODY-WEIGHT RATIO
	yr.	lb.	gm.	%
1	53	145	600	0.91
2	59	145	600	0.91
3	61	135	530	0.86
4	56	190	590	0.68
5	57	290	900	0.68
6	57	170	690	0.89
7	73	131	410	0.69
8	62	230	830	0.79
9	55	162	460	0.63
10	77	156	580	0.82
11	70	165	600	0.80
12	48	165	630	0.84
13	58	180	595	0.73
14	55	159	645	0.89
15	54	143	635	0.98
16	54	260	830	0.70
17	74	172	575	0.74
18	59	143	750	1.15
19	50	151	540	0.79
20	57	187	575	0.68
21	54	181	465	0.55

MATERIAL AND METHODS

In this study we reviewed the clinical and pathological records of 51 patients at the Veterans Administration Hospital in West Roxbury, Massachusetts. These represent all cases in which the

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pathological diagnosis of significant coronary arteriosclerosis was made during the five-year period ending with March, 1950.* Cases were excluded from this study in which causes other than hypertension or coronary sclerosis were present, such as valvular and syphilitic heart disease, myocarditis and cor pulmonale. All had pathological evidence of marked coronary sclerosis, with definite narrowing or obliteration of one or more of the coronary vessels.

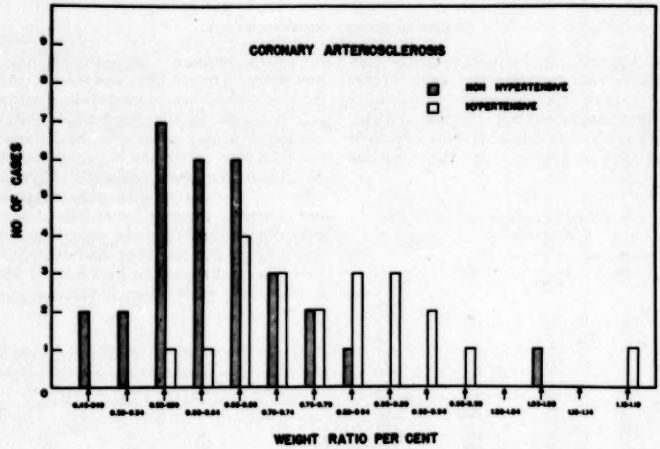

FIGURE 1. *Comparison of Heart-Weight: Body-Weight Ratios in Twos Groups of Patients with Coronary Arteriosclerosis.*

Patients with the combined diagnosis of coronary arteriosclerosis and hypertension were placed in a separate category. The causes of death varied and included myocardial infarction, congestive failure, carcinoma, tuberculosis and the like.

CRITERIA

Myocardial hypertrophy implies enlargement of the heart muscle beyond the normal range. There is extensive variation in the weight of healthy hearts, and separation of normal from abnormally heavy hearts is commonly made on the basis of statistically established limits. Published criteria for normal and enlarged hearts have differed, although there is fair agreement within a relatively wide range of weights. White[1] cites studies on 100 consecutive normal adult hearts in which the cardiac weight ranged from 160 to 380 gm. The average weight was 300 gm.; only 2 hearts exceeded 350 gm. in weight. Bardeen[2] considers a cardiac-weight-to-body-weight ratio of 0.55 per cent as the upper limit of normal; the New York Heart Association[3] states that cardiac hypertrophy is present when the heart weight exceeds 0.43 per cent of the body weight. Many pathologists report hypertrophy in any heart weighing more than 400 gm. For the purpose of this study the outer limit of normal was considered to be a heart-weight-to-body-weight ratio of 0.50 per cent. A figure exceeding this ratio was taken as evidence of hypertrophy.

RESULTS

The age, body and heart weight and heart-body ratio in the 30 cases of coronary arteriosclerosis without hypertension are tabulated in Table 1. Twenty-eight of these cases definitely satisfied the criteria for hypertrophy, the heart-body ratio exceeding 0.50 per cent. There were two cases with cardiac weights of 400 and 340 gm. that failed to surpass this ratio. At no time was the recorded blood pressure in excess of 150/90, despite repeated admissions or long periods of observation. The heart weight for this group of 30 cases of coronary arteriosclerosis without hypertension averaged 456.9 gm., with a range of 280 to 660 gm. The heart-weight-to-body-weight ratio ranged from 0.47 per cent to 1.07 per cent, with an average of 0.64 per cent. The average age for this group was 56.4 years. The problem of excluding hypertension as the cause of hypertrophy is admittedly a difficult one. Careful review of the

*All patients were males, with an average age of 56.7 years and with an age range of 38 to 75 years.

histories and clinical and autopsy findings revealed no evidence of hypertension in this group.

Twenty-one cases of the original 51 had the combined diagnosis of coronary arteriosclerosis and hypertension. The average age for this group was 59.1 years. All satisfied the criteria for hypertrophy. The heart weight averaged 620.4 gm., with a range of 410 to 900 gm. The heart-body ratio averaged 0.79 per cent, with a range of 0.55 to 1.15 per cent. The age, body weight and ratio of heart weight to body weight of this group of 21 cases are tabulated in Table 2. The fact that hypertension alone was not the sole cause of hypertrophy in this group can-

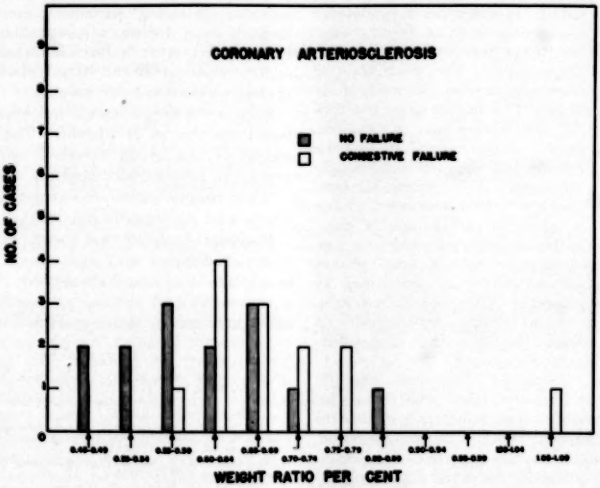

FIGURE 2. *Heart-Weight: Body-Weight Ratios in 27 Patients with Coronary Arteriosclerosis without Hypertension, According to Presence of Congestive Failure.*

not be excluded. The pathological diagnosis of hypertensive heart disease without significant coronary arteriosclerosis is, however, rare in our experience. Consequently, an adequate number for statistical comparison was not available. It is probably fair to say, however, that hypertension *and* coronary arteriosclerosis produce significantly larger hearts than does coronary arteriosclerosis alone. Figure 1 shows a comparison of the heart-body ratios of the two groups of patients with coronary arteriosclerosis.

Additional Factors

Three cases in the group of coronary arteriosclerosis without hypertension satisfied the criterion for hypertrophy by exceeding the heart-body ratio of 0.50 per cent but had cardiac weights of only 330, 325 and 280 gm. respectively. However, all three patients were described as emaciated, two dying of carcinoma and one of pulmonary tuberculosis. The association of a small heart with chronic debilitating disease has been described.[4]

Figure 2 shows the heart-body-ratio distribution of the 27 cases of coronary arteriosclerosis without hypertension (3 cases of debilitating disease have been excluded), tabulated according to the presence of congestive failure. The average heart weight in the congestive-failure group is 510.3 gm. and in the non-failure group 434.3 gm. The ratio for the former group is 0.70 per cent and that of the latter group 0.61 per cent. It is apparent that the combination of coronary arteriosclerosis and congestive failure tends to produce greater hypertrophy than does coronary arteriosclerosis alone. This has been previously described by Davis and Blumgart.[5]

Discussion

The unqualified concept of increased work as the sole cause for muscular hypertrophy is not confirmed by the weight of evidence. It is a mechanistic oversimplification that though apparently applicable in many cases plays no part in some. The common factor that is present in all cases is related more nearly to the *ability* of a muscle or organ to perform work than to the *amount* of work demanded of it. Apparently a disproportion must exist before

hypertrophy takes place. Thus stretching and straining of skeletal muscles (associated with pain and aching) eventually leads to enlargement of those muscles. The weight lifter does not develop his muscles by handling only those weights that are easily lifted. It is by straining against larger and still heavier burdens that the stimulus is provided that leads to hypertrophy. Likewise, the heart that must cope with persistent hypertension or valvular inefficiency begins to have increasing diastolic filling and systolic residue. When this assumes significant proportions (beyond the peak of Starling's curve) strain, stretching or dilatation takes place. Although this distortion may be subclinical, occasional episodes may be manifest as attacks of acute failure. In either event, persistence of exaggerated contraction resulting from greater initial length of the fibers eventually leads to increase in size, or hypertrophy. The same train of events follows, however, even when the work of the heart is not increased. This occurs when the contractile capacity of the myocardium is impaired. Thus increased diastolic volume develops in toxic and inflammatory states and when the blood supply to the muscles is impaired.[6] This concept has been summarized by Eyster,[7, 8] who has shown that factors that produce injury to cardiac muscle cause dilatation and that this in turn is followed by hypertrophy. This has been experimentally accomplished in rabbits by Katz and others[9] and confirmed by Hurwitz and Friedberg.[10] Therefore coronary inadequacy, which leads to impaired nutrition of muscle fibers, provides the injury that causes dilatation and consequent hypertrophy.

One phase of the concept is, however, obscure. This concerns the coronary system that though inadequate for existing myocardium is still able to permit the development of additional muscle tissue. This can be explained by the fact that coronary inadequacy is not ordinarily (except in status anginosus) a constant phenomenon. It becomes manifest at times when demands on the myocardium exceed the available coronary supplies. The injury that is the stimulus to hypertrophy occurs at these times. In the periods between such insults the coronary supply not only is sufficient for current metabolic needs but also permits hypertrophy to take place.

In general, the degree of hypertrophy is found to vary directly with the extent of coronary involvement.[5] Thus patients with the greatest vascular changes also have the heaviest hearts. This is particularly true when congestive failure has also been present.

Summary

The role of coronary inadequacy in the production of myocardial hypertrophy is not always entirely clear. This study concerns 51 patients who on pathological examination showed evidence of extensive coronary-artery disease. The causes of death were frequently of a noncardiac nature. Of these 51 patients, 30 had no history or showed none of the signs of hypertension. None had rheumatic or syphilitic heart disease, myocarditis or cor pulmonale. Of the 30 patients having only arteriosclerotic heart disease, unmistakable cardiac hypertrophy was present in 28. Two other hearts verged on hypertrophy (340 and 400 gm.) but did not exceed the heart-weight-to-body-weight ratio of 0.5 per cent.

Coronary-artery sclerosis and hypertension were found together in 21 patients. The average heart weight in this group exceeded by one third the average in patients with coronary disease alone.

When congestive failure was present at death the hearts were significantly heavier than in its absence.

It appears probable that uncomplicated coronary-artery inadequacy may and commonly does result in significant cardiac hypertrophy. This occurs as a consequence of hypoxic myocardial injury and subsequent muscle strain or dilatation.

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THE EFFECT OF ACTH IN TRICHINOSIS*

A Clinical and Experimental Study

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IN SOME areas, New England among them, trichinosis remains the most common parasitic disease of serious consequence.[1] A review of the cases occurring in Massachusetts in the ten-year period 1936–1945 reveals 287 cases, including 7 deaths.[2]

Trichinosis, as is well known, is produced by *Trichinella spiralis*, a small round worm that enters the body after the ingestion of pork or pork products containing encysted viable larvae. The cysts are digested and the larvae liberated. These develop into adult worms in the duodenum. After copulation the females invade the mucosa of the duodenum and deposit their eggs. The larvae that develop from these eggs invade the blood or lymph and are eventually carried to all parts of the body, invading skeletal muscle fibers and there becoming encysted.

The course of the disease is ordinarily divided into three stages. During the first stage, lasting a few days, the worms develop in the duodenum, causing localized irritative phenomena such as anorexia, nausea, vomiting and diarrhea. The second stage is the period during which the larvae enter the blood stream and are disseminated throughout the body, causing fever, leukocytosis, eosinophilia and inflammation of skeletal muscle, with pain and tenderness. This period may last for two weeks. The final stage is that of encystment of the larvae in the muscles; it corresponds clinically with the period of convalescence and gradual subsidence of symptoms and lasts four to six weeks or more. During the period of invasion and dissemination of the larvae, the disease is characterized by symptoms so pronounced as to suggest the action of a toxin or the presence of a severe allergic reaction on the part of the host. ACTH and cortisone are known to exert a dramatic effect in many diseases in which antibody-antigen reaction appears to play a major role.[3] The nature of trichinosis, — particularly its extreme toxicity and fever, together with the marked eosinophilia almost always present, — prompted the trial of ACTH in the 3 cases that came to our attention. Because of the favorable response in the clinical cases a study of the effect of ACTH therapy in experimentally infested animals was undertaken. The purpose of the study was to observe what changes, if any, might be observed in the course of the disease, particularly in its pathologic anatomy, to account for the clinical improvement noted in the patients treated. A fourth patient hospitalized with trichinosis during the same period was given no treatment because of the mildness of symptoms and the serious implications of ACTH therapy.

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CASE REPORTS

CASE 1. A 35-year-old woman was admitted to the hospital on August 24, 1950, complaining of fever, generalized muscular aches and pains and conjunctivitis. She had been well until 1 week before hospital admission, when she awoke with excessive lacrimation, swelling of the eyelids and pain in both eyes. At this time there was no fever, and these were the only symptoms elicited. An ophthalmic ointment containing Bacitracin was applied after consultation with her ophthalmologist. This afforded some symptomatic relief. Three days later there developed generalized muscular aches and pains and a spiking temperature. The face became swollen, particularly about the eyes, cheeks and lower eyelids. The temperature reached peaks of 102° and 103°F. The muscular pain grew worse, and at this time hospital admission was advised. On admission the diagnosis of trichinosis was considered and the patient's recent dietary history was obtained. Approximately 3 weeks before the onset of her illness the patient had prepared a roast of pork at her home and, together with several guests, had eaten it. After this she had had a bout of unexplained diarrhea. The guests were apparently unaffected.

Physical examination on admission showed a thin, well nourished woman in acute distress. The temperature was 103°F., the pulse 122 and the respirations 25. The blood pressure was 120/74. Marked swelling of the face, especially the eyelids, was seen. The muscles of the back and legs were tender and caused pain on movement.

Examination of the blood revealed 14,900 white cells with 67 per cent polymorphonuclear leukocytes, 25 per cent eosinophils, 6 per cent lymphocytes and 2 per cent monocytes. The hemoglobin was 16 gm. The total eosinophil count was 4300 per cu. mm. Other laboratory findings were noncontributory.

During the first 5 days in the hospital the general condition of the patient deteriorated. The temperature fluctuated between 101 and 106°, reaching peaks of 103, 103.4, 106, 104 and 105.5° respectively on these days. Treatment during this period included aspirin, alcohol sponge baths and Chloromycetin. On the sixth hospital day ACTH therapy was begun. This was administered in 10-mg. doses 4 times daily at intervals of 4 hours. Four hours after administration of the first dose the temperature fell to 98.4°. The eosinophil count performed on the day prior to the administration of ACTH was 10,300 per cu. mm. This fell to 3900 per cu. mm. 4 hours after the beginning of treatment. The pulse and respirations fell to normal levels. During the first day of treatment there was marked general symptomatic improvement, with diminution of muscle pain and soreness and lessening of fatigue. ACTH was administered in the same dosage for 6 days. The symptomatic improvement continued. The temperature reached peaks of 100, 100, 101, 100 and 98.6° respectively on the 2nd through the 6th day of treatment. The daily eosinophil counts performed during this period were 3900, 2600, 1900, 3500 and 2000 per cu. mm. The temperature, except for the peaks noted above, remained at normal levels, and the symptomatic relief from pain persisted. The complaints of the patient were easy fatigability and loss of strength. The swelling of the face gradually disappeared. On the 5th day of treatment a biopsy of gastrocnemius muscle was taken. This measured 5 mm. at its greatest diameter. Sec-

tions prepared from this specimen showed the presence of several larvae surrounded by an inflammatory exudate consisting mostly of mononuclear cells, with occasional neutrophils and eosinophils.

ACTH was discontinued after 6 days. A brief rise in temperature to 101.8° followed, with subsequent fall to normal levels on the ensuing four days. On the 14th hospital day the patient was discharged improved and resumed her normal activities.

CASE 2. A 35-year-old woman was first seen on August 19, 1950, in her home; she complained of fever and diarrhea of 2 days' duration followed by severe muscular aches and pains. The temperature had reached peaks of 104°. She complained especially of severe soreness and swelling of the eyes. Examination at this time showed an acutely ill woman. The conjunctivae were markedly thickened, and there was periorbital edema. The white-cell count at this time was 11,450, with 56 per cent polymorphonuclear leukocytes, 37 per cent eosinophils and 7 per cent lymphocytes.

Because of the similarity of symptoms between this case and Case 1, trichinosis was suspected. Inquiry into the recent dietary history revealed only one recent meal of pork. This was in the form of sausages, which had been consumed by the patient and her husband (Case 3). During the following 12 days the symptoms continued. There were severe generalized muscular aches and pains, with weakness and occasional bouts of dizziness. Bouts of fever, occurring particularly late at night, were followed by drenching sweats. On September 1, 1950, approximately 2 weeks after the onset of symptoms, ACTH therapy was begun. The temperature at this time was normal. The white-cell count was 11,250, with 55 per cent polymorphonuclear leukocytes, 35 per cent eosinophils and 10 per cent lymphocytes. The total eosinophil count was 3800 per cu. mm. ACTH was administered in 10-mg. doses 4 times daily for 6 days. After the first day of therapy there was dramatic symptomatic improvement, with almost complete relief of fatigue, weakness and muscular pain. This improvement persisted during the entire course of treatment. On September 10, 1950, a trichina skin test was performed; this was strongly positive in 10 minutes. During the following several weeks the only complaint was occasional weakness and a sense of fatigue.

CASE 3. A 35-year-old man was seen for the first time, together with his wife (Case 2), on August 19, 1950, complaining of swelling of the eyes, headache, fever and severe muscular aches and pains. He had had bouts of profuse diarrhea similar to those of his wife. The white-cell count was 17,050, with 23 per cent polymorphonuclear leukocytes, 65 per cent eosinophils and 12 per cent lymphocytes.

During the ensuing 12 days the symptoms continued without much change. There was low-grade fever, severe muscular pain and a persistence of swelling and injection of the eyelids. On September 1, 1950, ACTH therapy was begun. This consisted of 40 mg. daily, in doses of 10 mg. at intervals of 4 hours. Within 24 hours there was marked symptomatic improvement. The patient was able to sleep for the first time in ten days. Within 48 hours the generalized muscular aches and pains, as well as the periorbital edema and conjunctival chemosis, had disappeared. Some weakness and diarrhea persisted during the first 3 or 4 days, but by the 6th day of ACTH therapy the stools were again normal. ACTH was discontinued after 6 days. The subjective improvement continued, although the patient complained of weakness. A trichina skin test performed on September 10, 1950, was markedly positive within 10 minutes. Improvement continued, and the patient felt strong enough to return to work on September 17, 1950.

EXPERIMENTAL STUDY

Materials and Methods

The guinea pig was chosen for the study because of its marked susceptibility to experimental infestation by *Trichinella spiralis*. Since the purpose of the study was to demonstrate, if possible, any alteration by ACTH in host response to severe infection by trichina, the numbers of larvae administered to the animals were in all cases in excess of what is ordinarily considered a lethal dose for guinea pigs.[4] Young guinea pigs weighing approximately 250 gm. were selected and placed on a uniform diet. These animals were observed for 1 week for evidence of disease. Rat muscle infested with the encysted larvae of *Trichinella spiralis* was digested after the method of Bozicevich, using a solution of 0.5 per cent hydrochloric acid and 0.7 per cent pepsin at 37°C. for five hours. The digest was filtered through a screen and the liberated larvae allowed to settle out by gravity. A suspension of larvae containing an average of 2250 per cc. was then prepared. Thirty-two healthy guinea pigs were selected and weighed; white-cell counts, eosinophil counts and differentials were made. These animals were then given graded doses of the larvae by gavage after food and water had been withheld for twenty-four hours. Group 1, comprising 20 animals, was given graded doses of larvae ranging from 15 to 55 larvae per gm. of body weight (1.5 to 6 cc. of the suspension). Group 2, comprising 12 animals, was given extremely large doses consisting of 10 cc. of the suspension, or a total of approximately 22,500 larvae.

Thereafter the animals were observed daily for diarrhea and fever. White-cell counts and eosinophil counts were determined and blood smears made throughout the course of the experiment at three-day intervals. As the Group 1 animals began to manifest high fever associated with significant eosinophilia 50 per cent were segregated and given ACTH, 10 mg. daily divided into 4 equal doses. The rest of the group were given no treatment. Half the experimental animals in Group 2 were given 12 mg. of ACTH daily commencing forty-eight hours after the administration of the larvae. In both groups, treated and untreated, were animals that had been given equivalent doses. Muscle biopsies were taken on representative animals at the height of the eosinophilia and fever. Autopsies were performed on all the animals that died. Tissues were fixed in Zenker's solution and in 10 per cent formalin and the sections stained with hematoxylin and eosin; others were stained with phloxine-methylene blue.

EXPERIMENTAL RESULTS

Initially the rectal temperatures of the animals averaged 101.6°F., with a range of 100.4 to 102°F.; the leukocytes averaged 7320, with a range of 5100 to 10,450; the eosinophil count averaged 80, with a range of 25 to 150.

Group 1

The clinical observations were limited to the rectal temperatures and the presence or absence of diarrhea. All animals exhibited some degree of diarrhea, with a concomitant rise in temperature on the second and third days after the administra-

tion of larvae. Eight animals receiving doses of 5 to 6 cc., identified as Group A-1, had appreciably more dysenteric activity and fever than those that had been given smaller amounts; fevers up to 103.2°F. were recorded for two days. Thereafter the rectal temperatures showed sporadic small elevations for a week, followed by a trend toward steady elevation. By the fourteenth day, temperatures over 104°F. were recorded. On the sixteenth day half of these animals were placed on ACTH. Within twenty-four hours the average recorded temperature had fallen from 104.2 to 102.4°F. Thereafter these treated animals showed minor occasional elevations in temperature for a period of eight days, after which the temperature gradually increased. This treated group died between the twenty-sixth and twenty-seventh days, except for one animal that survived for two months and was eventually sacrificed.

The animals in Group 1-A that received no treatment followed a similar course up to the sixteenth day. Thereafter fever continued at high levels, (104 to 105°F), and all died during the next seventy-two hours.

Group 1-B comprised 12 animals that had received doses of 1.5 to 4 cc. of the larval suspension. The onset and course of fever in this group was nearly identical to that of the group receiving larger doses, except that it lagged by several days — that is, the significant rise began on about the twentieth day and reached a peak on the twenty-fourth day, when treatment was started. ACTH administration caused a similar temporary drop in fever. The treated half of this group died between the thirty-fifth and forty-sixth days; the untreated animals died between the twenty-sixth and fortieth days.

Group 2

Half of the animals in Group 2, — those receiving the largest doses (10 cc. of the suspension of larvae), — were merely given 12 mg. of ACTH daily after administration of the larvae and maintained thereon for twenty-eight days. All the animals in this group died within four days after withdrawal of ACTH; the untreated animals all died between the sixteenth and twenty-fourth days.

All the animals that received ACTH showed a temporary but striking fall in the number of circulating eosinophils. For example, those animals receiving doses of 5 to 6 cc. showed a gradual increase in the number of eosinophils, averaging 930 on the fifteenth day after infestation with larvae. After forty-eight hours of ACTH therapy the treated members of this group showed an average eosinophil count of 98. However, this fall did not persist, and within three days the counts averaged 1800. Thereafter, in spite of the administration of ACTH, there was a gradual rise, reaching a peak of 2400 on the twenty-fourth day. The untreated animals in this same group showed an average eosinophil count of 890 on the fifteenth day. The rise thereafter was gradual, reaching a peak average of 4050 on the seventeenth day. None of these untreated animals survived beyond the nineteenth day.

The muscle-biopsy specimens taken at the height of eosinophilia and at intervals during ACTH therapy and those obtained at autopsy were studied microscopically in order to ascertain whether or not ACTH altered the appearance of the larvae or the process of encystment. No apparent differences in morbid anatomy between treated and untreated animals was demonstrable. Both groups showed little inflammatory response to the larvae in the muscles, and the process of encystment was similar in both groups. The numbers of successfully encysted larvae in treated and untreated animals receiving equivalent doses were similar, although no actual counts were made to prove this.

Discussion

The rather dramatic symptomatic improvement in the three clinical cases, — particularly the striking diminution of muscle tenderness and fever, — suggested the possibility that the host response to *Trichinella spiralis* might be fundamentally altered by ACTH therapy and that anatomic studies of the disease during such treatment would reveal objective evidence of changed host response. Microscopical observations of the experimentally produced lesions showed no detectable anatomic change in the larvae themselves or in the encystment and inflammatory response on the part of the host tissues. This is in keeping with observations made by others that fundamentally the course of diseases responding favorably to ACTH and cortisone may not be demonstrably altered. Even if this is true, any consideration of the treatment of trichinosis must take into account the fact that the disease is self-limited by its very nature. The host must perforce suffer the migration, encystment or destruction of whatever larvae are liberated by the gravid females within the intestinal mucosa. Short of enhancing the power of the host to destroy the larvae by chemotherapeutic methods, it appears that at this time ACTH affords a favorable opportunity of altering the severe toxic manifestations of a disease that inevitably passes through a definite cycle. Finland and Kass have demonstrated that ACTH possesses a definite antipyretic effect and warned against overly optimistic interpretations of clinical responses to ACTH and cortisone.[5] However, the results obtained in the treatment of our 3 cases of human trichinosis appear to be at least comparable to those obtained in diseases in which Thorn and his co-workers[3] consider the administration of ACTH "useful," although its effects are obviously nonspecific.

Summary and Conclusions

Three patients seriously ill with trichinosis were treated with relatively small doses of ACTH, with

striking diminution of subjective symptoms. This response was accompanied by a similarly striking loss of fever and a temporary fall in the number of circulating eosinophils.

Guinea pigs experimentally infested with *Trichinella spiralis* were treated with ACTH. Study of the lesions in treated and untreated groups of animals revealed no demonstrable anatomic difference either in the larvae themselves or in the reaction to them on the part of the host. There appeared to be a reduction of toxic effects of the disease in animals treated with ACTH, together with temporarily diminished eosinophilia. One treated animal survived a severe infestation; the other treated animals survived for significantly longer periods than those receiving no treatment. ACTH appears to alter favorably the clinical course of trichinosis.

The purpose of the study was to demonstrate, if possible, any alteration in host response to infection by trichina. No anatomic changes were noted. The numbers of larvae administered in the present study were in all cases far in excess of minimum lethal dosage and the administration of ACTH did not decrease the mortality under these conditions.

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FATAL TRANSFUSION REACTIONS FROM MASSIVE BACTERIAL CONTAMINATION OF BLOOD*

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THE sterility of stored whole blood depends on three factors: aseptic technic, a sterile system for collection and storage and immediate, continuous refrigeration. These measures are highly effective for preserving blood in a relatively sterile state. Nevertheless, under certain circumstances, gross bacterial contamination of stored blood can occur. Although the essential features of accidents resulting from the administration of contaminated blood are mentioned by Whitby,[1] detailed descriptions are not available.

The administration of contaminated blood produces a characteristic clinical syndrome that may be incorrectly interpreted. There is reason to believe that transfusion reactions due to bacterial contamination have occurred more frequently than is realized. The actual incidence of such reactions can never be assessed if these accidents are not recognized and reported. It is the purpose of the following account to present two cases of fatal reactions from the transfusion of grossly contaminated blood, with emphasis on bacteriology, diagnosis and prevention.

Case Reports

Case 1. A 23-year-old Indian entered the hospital on August 18, 1948, because of a generalized pyoderma of 2 weeks' duration. He was acutely ill and had a vesicular eruption involving the face, trunk and extremities. The temperature was 102°F., the pulse 120 and the blood pressure 120/70. Examination of the blood revealed a hemoglobin of 11 gm. per 100 cc. and a red-cell count of 3,850,000. Culture of the blood yielded no growth.

Although the pyoderma improved slightly with therapy, the mild anemia persisted. A transfusion of compatible Group A, D-positive blood was started at 11:00 a.m. on September 10, 1948. At 12:05 p.m., after 375 cc. had been administered, the patient suffered a violent chill lasting 40 minutes. His temperature rose to 104°F. and the pulse rate to 160; the blood pressure fell to 60/0. A specimen of urine obtained at 12:50 p.m. contained no hemoglobin. The plasma hemoglobin concentration was 6 mg. per 100 cc., a value that eliminated intravascular hemolysis as a cause of the reaction. The patient was nauseated and developed vomiting and watery diarrhea. Both emesis and stool contained streaks of blood. The pulse and blood pressure could not be obtained at 3:00 p.m., although the patient was mentally alert. His extremities were warm and slightly moist. The circulatory collapse did not respond to supportive therapy and he died at 6:30 p.m., 6½ hours after transfusion was begun. Permission for autopsy was denied. A culture of the patient's blood obtained shortly after death yielded no growth.

Bacteriologic studies. Gram stains of smears of the remaining contents of the transfusion bottle revealed large numbers of non-spore-forming, gram-negative bacilli. Cultures in nutrient broth and on blood-agar plates showed identical bacilli. They grew slowly in an incubator (37°C.), rapidly in a refrigerator (5°C.) and most rapidly at room temperature (28°C.). The organism was identified morphologically and biochemically as belonging to the genus *Achromobacter*. The identification was confirmed by the Medical Laboratories of the Minnesota Department of Health and by the Department of Bacteriology of the Army Medical Department Research and Graduate School.

When removed from the refrigerator (5°C.), the supernatant plasma of the donor blood revealed no gross hemolysis. It was proved by experiment that the contaminating organism did not cause lysis of human blood cells at 28°C. or 37°C. However, when warm blood-agar cultures were chilled at 5°C., a broad zone of hemolysis developed about each bacterial colony. It seemed clear that this organism might grow rapidly in blood only when warmed to room temperature

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(28°C.) but would cause hemolysis only if the blood were subsequently cooled (5°C.).

The organism was avirulent for guinea pigs. It was killed by autoclaving at 121°C. for 20 minutes. It was not sensitive to 50 units of streptomycin or penicillin per cc. in vitro.

CASE 2. A 38-year-old-truck driver entered the hospital for removal of a herniated intervertebral disk. An operation was begun at 8:00 a.m. on September 21, 1948. At 9:30 a.m. a transfusion of compatible Group 0, D-positive blood was started; 500 cc. had been administered by 11:00 a.m. No untoward reaction was apparent. The blood pressure was 115/55. One hour later, after the patient had been returned to bed, the blood pressure fell to 80/60. The pulse rate was 110 and the temperature 102°F. The fingers and hands were cyanosed. Plasma and urine hemoglobin determinations were normal.

Parenterally administered fluids and an additional 700 cc. of whole blood failed to elevate the blood pressure. There was a temporary rise to normal levels after the intravenous administration of neosynephrine, but further doses of vasoconstrictor agents had no effect. The blood pressure thereafter was seldom above 70/40; on several occasions it was unobtainable. The hemoglobin remained at 14.8 gm. per 100 cc.

On the following day the physician who had seen the patient described in Case 1 examined this patient. At his request direct smears of the remaining contents of the bottle of blood given during operation were examined; they were found to be loaded with gram-negative bacilli. Penicillin and streptomycin therapy were instituted. The rectal temperature fell from 103°F. to 100°F.; it remained at 100°F. until the following evening, when it rose to 104°F. The patient was restless, apprehensive and at times disoriented. The respirations were rapid and shallow. The pulse was weak and thready. The extremities were cold and cyanotic. A small amount of bloody mucus was passed by rectum.

Only 50 cc. of urine was obtained by catheter immediately after operation. Thereafter anuria developed. On the second postoperative day the blood urea nitrogen was 62 mg. per 100 cc. and the carbon-dioxide combining power was 29 vol. per cent. The spleen became palpable. The patient vomited a large quantity of dark-brown material. He died shortly thereafter, 60 hours after the transfusion of contaminated blood.

Autopsy revealed pulmonary edema; the right lung weighed 1210 gm. and the left 1200 gm. The spleen was congested and weighed 500 gm. The heart was normal in size; there were several subepicardial and subendocardial petechial hemorrhages. No ulcerations were found in the gastrointestinal tract. The kidneys were normal. There was a decrease in the number of vacuoles in the cells of the adrenal cortex.

Bacteriologic studies. The first blood-transfusion bottle was examined 24 hours after the transfusion was completed. Smears of the remaining blood revealed large numbers of gram-negative, non-spore-forming, motile bacilli in clumps. Cultures grew well at 37°C. and 28°C., but only slight growth occurred at 5°C. The organism was identified morphologically and biochemically as *Paracolobactrum aerogenoides.*

A small tube of blood attached to the transfusion bottle and used for typing and cross-matching purposes was also examined. It had been entered previously with an unsterile applicator stick, but smears revealed no bacilli and cultures showed only coagulase-negative staphylococci. The second and third bottles of blood given to this patient revealed no evidence of bacterial contamination.

A culture of venous blood obtained from the patient on September 22, 1948, revealed bacteria identical with those recovered from the blood in the first transfusion bottle. An identical organism was recovered from the heart blood and spleen of the patient at autopsy. None of the four strains were sensitive to 50 units of penicillin per cc. but all were sensitive to 2 units of streptomycin per cc. in vitro. The patient's venous blood contained 30 units of streptomycin per cc., but the bacteremia was not eliminated — presumably because of the massive contamination and the formation of multiple infected foci in the spleen and other organs.

The organism was readily killed by heating in an autoclave at 121°C. for 20 minutes. It grew only slowly in fresh clotted normal human blood at 28°C. but grew much more rapidly in blood to which acid-citrate-dextrose solution had been added. This presumably was partly due to inactivation of complement and prevention of serum bacteriolysis. In addition, the citrate may have acted as a specific growth stimulant.

PROBABLE SOURCE OF CONTAMINATION

The blood causing these transfusion accidents was obtained from a central bank in another city. It was shipped in refrigerated cartons. The temperature inside the cartons on arrival was 10°C. and the blood was approximately forty-eight hours old. It was then stored in a refrigerator with an average temperature of 7°C. The unit causing the first accident was eighteen days old when administered and that causing the second was twelve days old.

Bacteremia in the donors at the time of bleeding had been excluded insofar as both donors had normal temperatures and negative medical histories and physical examinations. Since pilot tubes are usually filled with blood from the donor tubing, failure to recover the organism causing the second death from the pilot tube attached to the bottle tended to eliminate the blood of the second donor, his skin and the tubing used to draw the blood as possible sources of the contamination.

The blood was dispensed in reclaimed bottles that were processed in the laboratory of the central bank. The bottles were mechanically evacuated and sealed with an inset rubber stopper that was held in place by a metal screw cap. Lots of 100 to 150 bottles were sterilized for twenty minutes after the temperature of the autoclave exhaust line reached 121°C. Reliance for sterility was placed on a color tab indicator that was attached to each bottle, and those bottles not used within a week were resterilized.

Over 3000 units of blood from this bank had been given without a serious reaction. Thirty-five units bore the same expiration date as that causing the first death; 9 units bore the same date as that causing the second. No unusual reactions were reported from other institutions drawing on the same source. The 2 grossly contaminated units of blood and resulting deaths were apparently isolated instances.

PYROGEN STUDIES

Achromobacter Sp.

It was demonstrated in rabbits that this organism produced a pyrogen. A culture grown in rabbit blood with acid-citrate-dextrose solution was injected intravenously. A maximum rectal temperature of 42°C. was attained within one to three hours; it then declined rapidly. The animals became weak and their respirations labored; most of them died within a short time. Blood cultures were sterile. Death could not be attributed, therefore, to septicemia but appeared to result from the toxicity of the bacterial pyrogen.

Paracolobactrum Aerogenoides

This bacterium produced a more potent pyrogen. Cultures grown in rabbit blood with acid-citrate-dextrose solution proved more toxic to rabbits than any other preparation. After intravenous injection their rectal temperature rose 2 to 3°C. The rabbits became weak and lethargic. Rapid respirations, cyanosis and profuse diarrhea occurred regularly. Convulsions and death frequently resulted. The manifestations of toxicity were remarkably similar to those observed in the human being. Autopsy revealed no disease. Bacterial growth in rabbit blood led in each instance to some hemolysis in vitro. However, the kidneys of rabbits dying after inoculation with such cultures did not contain hemoglobin casts. The great toxicity of such cultures appeared to be due to the heavy bacterial population.

The pyrogen in both cultures was not inactivated by heating at 121°C. for twenty minutes. The pyrogen was also present in Seitz filtrates of broth cultures. It is generally recognized that bacterial pyrogens in solutions cannot be inactivated in an autoclave and that they cannot be removed by filtration through the usual bacterial filters.

Purified pyrogen was prepared by the method of Shear and Turner.[2] A protein-free substance was obtained, presumably polysaccharide in nature. It was moderately pyrogenic in rabbits. Intravenous administration of only 4 microgm. per kg. of body weight sufficed to produce a rise in rectal temperature of 1.2°C. A dose 50 times larger, however, produced no greater fever. This extract seemed less toxic than washed bacilli to rabbits.

A pyrogenic extract was also prepared by the method of Robinson and Flusser.[3] This material was capable of producing tachypnea and fever in rabbits, but even in large doses it failed to produce the same shock syndrome seen when whole bacterial cells were used.

Circulatory Studies

It was possible to produce experimentally in dogs the shock syndrome observed clinically. Two animals injected with forty-eight-hour cultures of the Achromobacter species sustained a rather prompt fall of blood pressure and cardiac output, which then tended to return toward control levels. Four animals injected with cultures of *Paracolobactrum aerogenoides* developed a progressive fall of arterial pressure and cardiac output. There was also a moderate decrease in plasma volume, with slight hemoconcentration, which did not entirely account for the rather marked reduction in cardiac output.

The altered hemodynamics observed in this study were almost identical with those reported by Aub and his co-workers[4] in experimental shock produced by the injection of traumatized muscle exudate contaminated with Clostridia. The endotoxins present in most gram-negative bacilli have been shown to be severely injurious to capillary and other blood-vessel walls.[5-7] The primary circulatory disturbance in bacteremic shock is probably due to the effects of bacterial pyrogens on the peripheral vascular bed.[7] A very small dose of purified pyrogen from *Eberthella typhosa* has produced a severe shock syndrome in a human subject.[8] Purified pyrogens have also been shown to produce marked hypotension without fever.[9]

Discussion

The clinical features and bacteriologic findings in two deaths from the transfusion of grossly contaminated blood have been presented in detail. The first patient developed a violent chill followed by high fever, tachycardia and vascular collapse after transfusion of 375 cc. of blood grossly contaminated with the species Achromobacter. Nausea, vomiting and diarrhea were prominent symptoms. Death occurred in six and one-half hours. At the time of death the blood stream had been cleared of organisms, as post-mortem blood cultures were sterile. The second patient received during an operation 500 cc. of blood that was grossly contaminated with *Paracolobactrum aerogenoides*. Symptoms were modified by anesthesia. Fever, tachycardia, hypotension and cyanosis did not appear until two and one-half hours after the transfusion was started. The shock syndrome did not respond to therapy and resulted in anuria and uremia. Death occurred sixty hours after the transfusion. The marked pulmonary edema found at autopsy was partially attributable to too vigorous parenteral fluid therapy. The contaminating organism was recovered from the patient's blood during life and from the heart blood and spleen at autopsy. Bacteremia had persisted despite more than adequate blood levels of streptomycin.

Data for available case reports of reactions to contaminated blood or plasma are given in Table 1. It is apparent that a small quantity of contaminated blood (as little as 40 cc.) can result in speedy death. The symptoms produced by the infusion in most cases closely resembled those observed in Case 1 of this report. Rigor and high fever invariably occurred, followed by tachypnea, tachycardia, hypotension and cyanosis in the majority of cases. Abdominal distress, vomiting and diarrhea are significant symptoms when present. Both emesis and stool may contain blood. Initially the extremities may be warm, but when hypotension becomes profound the classic shock syndrome, with cold clammy extremities, oliguria and stupor, supervenes. Death apparently results from peripheral vascular collapse.

A detailed account of an episode of mass bacterial contamination of banked blood observed in Britain during World War II has been furnished by Sir Lionel Whitby.[10] Faulty sterilization and insuffi-

cient refrigeration resulted in the massive contamination of 12 out of 20 bottles of blood. Three patients received this blood before the contamination was discovered; 2 died and 1 was severely ill for forty-eight hours. The blood administrated to each appeared macroscopically normal. The contents of all 17 unopened bottles in the lot were cultured. Five contained coliform bacilli alone; 2 contained coliform bacilli and *Pseudomonas aeruginosa* and 2 contained *Ps. aeruginosa* alone. Gram-negative bacilli were demonstrated by direct smear of the remaining contents of all the contaminated bottles. All strains isolated by culture were proved to be capable of growth at refrigerator temperatures; none gave rise to macroscopic hemolysis in media containing blood. Another disaster of this kind occurred on the Middle Eastern front, costing the lives of 4 patients. Due to confusion a batch of 20 bottles escaped the autoclave, with the result that 19 units of blood were contaminated with *Escherichia coli*. None of these units showed evidence of macroscopic hemolysis.

The data in Table 1 point up the fact that the organisms found in grossly contaminated blood have been predominantly gram-negative, non-spore-forming enteric bacilli. Gram-positive cocci were isolated in only one reported instance involving blood.[14] Enteric bacilli are ubiquitous in nature. They may be found on the skin but are commonly found in feces, soil and surface water. Those that do not form spores cannot be regarded as aerial contaminants. They seldom cause septicemia. Their ability to grow at low temperature and their ability in certain cases to utilize citrate account in part for their multiplication in stored blood.

Bacterial contaminants may enter stored blood in 3 ways: They may be introduced from the skin or blood stream of the donor; they may gain entry through an imperfect seal in the bottle cap; and unsterile bottles or donor equipment may provide an inoculum of viable organisms.

Although it is impossible to sterilize completely the skin of the donor, the degree of contamination arising from this source is slight and ordinarily provides a bacterial inoculum that is too small to grow under the conditions prevailing in refrigerated blood. Moreover, enteric organisms such as the species Achromobacter isolated in Case 1 of this report almost never produce asymptomatic bacteremia in man and therefore are not likely to be found in the blood of the healthy donor.

It has been shown that some leakage of air into vacuum bottles closed with a screw cap may occur regardless of precautions taken to ensure a tight fit.[16] Although contamination by air is a possibility, the organisms that have been found in seriously contaminated blood have not been common airborne species.

Water and soil organisms are known to be frequent contaminants of equipment and glassware in the milk industry. These organisms can also be cultivated from washed blood bottles and rubber tubing prior to autoclaving.[15] The British experience cited earlier clearly demonstrated that when autoclave failure results in mass contamination of stored blood the contaminant is invariably a coliform (enteric) organism. The occurrence of "cold spots" in large autoclaves as a cause of isolated instances of contamination is generally well known. It seems probable that the isolated instances of contaminated blood that form the basis of this report were due to failure of the autoclave to sterilize bottles that harbored an inoculum of bacteria.

The prevention of contamination of stored blood requires meticulous technic during bleeding, careful selection of donors, proper cleansing of the skin and use of a "closed" system with hermetically sealed bottles. From the foregoing account it follows that the most important element is absolutely sterile donor equipment and blood bottles. Both the reported instances of contamination of blood and the experiences described herewith involved

TABLE 1. *Summary of Reported Cases of Reactions Due to Bacteria-Contaminated Whole Blood or Plasma.*

AUTHOR AND DATE	NO. OF CASES	MATERIAL	VOLUME	ORGANISM	OUTCOME
			cc.		
Strumia and McGraw[10] 1941	4	Plasma	200	Gram-positive, non-spore-forming bacillus	
			200		Recovery in 2 hours
			200		Recovery in 2 hours
			80		Recovery in 4 hours
			(100 & 200)		Recovery in 4 hours
Weinstein[11] 1942	1	Plasma	75	*Staph. albus*	Recovery
Officer[12] 1942	1	Blood		*E. coli*, Strep.	Death during transfusion
				Anaerobic bacilli	
Mollison[13] 1943	1	Blood	40	Unidentified	Death in 12 hours
Cofré[14] 1944	1	Plasma		Anaerobic, gram-positive coccus	Death
Whitby[15] 1949 (Britain).....	3	Blood	120	*E. coli*	Death in 3 hours
			50	*E. coli, Ps. aeruginosa*	Death in 9 hours
			50	*E. coli, Ps. aeruginosa*	Recovery in 48 hours
Whitby[15] 1949 (Middle East) ...	4	Blood		*A. aerogenes*	Death in 1 to 4 hours
Borden and Hall 1951	2	Blood	375	*Achromobacter* species	Death in 6½ hours
			500	*Paracolobactrum aerogenoides*	Death in 60 hours

bottles that were processed in hospital or blood-bank laboratories. All these accidents occurred before disposable bottles and tubing were in general use. Elaborate tests for sterility, pyrogens and chemical purity are necessary to ensure safety of blood bottles and parenterally given solutions. The mass production of uniformly sterile equipment, parenterally administered fluids and blood bottles requires accurate timing in processing methods and rigid controls that would be impractical and are not generally available in the average hospital or blood-bank laboratory. The use of commercially prepared disposable donor equipment and disposable blood bottles helps to eliminate the most obvious source of bacterial contamination. Disposable units are to be recommended for reasons of safety, convenience and economy.

Bacterial growth in stored blood is best retarded by immediate and continuous refrigeration. Although low temperatures prevent growth of the usual organisms arising from the skin of the donor (staphylococci), coliform bacilli may multiply rapidly under such conditions. Fresh human blood kills the latter organisms readily at body temperature, but at refrigerator temperature the bacteriolytic process is inactivated. At low temperatures bacteria may unite with bactericidal antibody, but complement is not bound and therefore bacteriolysis does not occur.[17] Various chemical preservatives added to stored blood have been shown to be unreliable in preventing bacterial growth in nontoxic concentrations.[18]

Verbal reports concerning the British experience with contaminated blood led to the correct diagnosis of the first case in this report. The second case was not recognized until seen by a physician familiar with the first. The cardinal feature of reactions due to the administration of contaminated blood is peripheral vascular collapse. As illustrated by the second case, other characteristic symptoms may be modified and delayed by factors such as anesthesia. The vascular collapse may then be wrongly attributed to either the primary disease under treatment or to hemorrhage or trauma and procedures necessary to establish the correct diagnosis may not be undertaken.

The key to the proper investigation of transfusion reactions is the immediate determination of the plasma hemoglobin concentration to establish the presence or absence of intravascular hemolysis.[19, 20] In addition, the transfusion bottle and tubing should be retained unopened in the laboratory for twenty-four hours so that sufficient material may be available for the subsequent investigation of blood groups both in case of a hemolytic reaction and for purposes of bacteriologic study. Bacteriologic study should include direct smears of the remaining blood and cultures at both room temperature and incubator temperature. Direct smears are of extreme importance because by this means gross bacterial contamination can be diagnosed immediately and appropriate therapy instituted without delay and the degree and type of contamination can also be estimated.

Detection of bacterial contamination in stored blood or its products is a problem for which no satisfactory solution has been found. Any gross hemolysis as revealed by inspection of the supernatant plasma should preclude the use of the blood. Hemolysis, however, is an unreliable index of contamination, as many bacteria produce no hemolysis. In both the British experience and our own, none of the contaminated units of blood showed macroscopic evidence of hemolysis. Mollison has pointed out that hemolysis may not be apparent in stored blood until the sedimented cells are resuspended and a specimen centrifuged.[19] Examination of each unit of blood by means of stained smears or cultures is impractical. If applied to small samples, it is subject to sampling errors and may itself lead to contamination. It is therefore not recommended as a routine procedure.

Treatment of reactions from contaminated blood is difficult, as the organisms involved are often resistant to most antibiotic agents. Even though the bacteremia is controlled, death can still occur from the toxic effects of the bacterial pyrogens on the vascular system, as illustrated by the first case in this report. The circulatory failure produced by bacterial pyrogens is not related to a significant reduction in total blood volume and is not beneficially altered by transfusion therapy.[21] These accidents are obviously best avoided and can only be prevented by strict control of each procedure involved in the collection and storage of blood.

Summary and Conclusions

Two deaths from the transfusion of blood grossly contaminated with gram-negative bacilli are reported. Death was preceded by a shock syndrome accompanied by chill, fever, vomiting, diarrhea and cyanosis. The clinical manifestations in the second case were modified by anesthesia and surgery. Proper diagnosis was dependent on the clinical recognition of the peripheral vascular collapse, the exclusion of intravascular hemolysis by a plasma-hemoglobin determination and the availability of the transfusion equipment for bacteriologic study.

Direct smears and cultures (28°C.) of the blood remaining in the transfusion bottle demonstrated large numbers of Achromobacter species in the first case and of *Paracolobactrum aerogenoides* in the second. These organisms were capable of rapid growth at low temperatures in preserved blood and did not produce macroscopic hemolysis. Experimental studies proved that these organisms produced potent pyrogens.

The circulatory failure produced in dogs by the injection of these organisms was characterized by a marked lowering of blood pressure and cardiac

output, with a slight reduction in plasma volume. This vascular collapse probably resulted from the injurious effects of the bacterial pyrogens on the peripheral vascular bed.

In serious reactions to contaminated blood that have been reported to date, the predominant organisms have been coliform bacilli. The probable source of contamination in most instances was unsterile glassware resulting most likely from autoclave failure.

The prevention of gross bacterial contamination of blood depends primarily on elaborate controls to ensure sterility of bleeding equipment and storage bottles. Minor degrees of bacterial contamination of stored blood are always a possibility; they are best controlled by rigid asepsis in blood collection, use of bottles with a hermetic seal and continuous refrigeration of the stored blood.

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DIABETIC COMA VERSUS DIABETIC NEPHROPATHY*

Hazards of Factitious Insulin Resistance, Oliguria and Hyperkalemia

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DIABETIC nephropathy has become the most serious late complication of childhood diabetes. After ten or more years of imperfect control, diabetes is accompanied by edema, albuminuria, hypertension, retinitis and finally uremia. The characteristic findings in the kidneys are arteriolosclerosis, particularly of the afferent arterioles, intercapillary glomerulosclerosis (Kimmelstiel–Wilson), pyelonephritis, generalized arteriosclerosis and usually some lesions of glomerulonephritis. Diabetic coma or severe acidosis has usually occurred one or more times during the earlier years of the patient's diabetes. The development of excessive ketone bodies in the blood and the characteristic air hunger, dehydration, acidosis and shock characterize diabetic coma in contrast to uremia.

The diagnosis and treatment of unconsciousness in a diabetic child or youth requires adequate laboratory data promptly obtained and correctly interpreted. Clinical judgment and experience may suffice in emergencies in the absence of such data, but grave errors frequently occur when laboratory facilities are not utilized. The following two case reports from the New England Deaconess Hospital illustrate rapid treatment of a child in diabetic coma without the use of glucose or potassium solutions and the diagnostic problems afforded by a young diabetic in whom uremia simulated ketosis and in whom fatal hyperkalemia occurred.

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Case Report

CASE 1. B. S., a 6-year-old girl, was first known to have diabetes when found in coma, with a blood sugar of 1060 mg. per 100 cc. on November 27, 1950. Six weeks earlier weakness, listlessness and increased thirst had first been noticed. Table 1 summarizes her record. On admission she was entirely unconscious, and shortly thereafter the nurse recorded that she was pulseless. Her breathing was deep and rapid, with marked dehydration of the tongue, lips, axillas and skin. Subsequently the pulse varied between 130 and 150 and the blood pressure was 80/50. Examination of the heart, lungs and abdomen was negative, but the temperature was 102°F. No explanation for the fever was found at x-ray examination of the chest or microscopical examination of the urinary sediment.

Improvement was rapid. By 4:00 p.m. the patient responded and her respiration was less rapid, although air hunger was

still evident. By 8:00 p.m., when the blood sugar had fallen from the original level of 1060 mg. to a normal value of 103 mg., she was alert. By midnight she was able to retain 10 gm. of carbohydrate per hour in the form of fruit juices, oatmeal gruel and the like.

An electrocardiogram made about 5:00 p.m. on November 27 showed regular sinus rhythm with a rate of 122 with a PR interval of 0.12 second and a QT interval of 0.35 second. The T waves were upright in the first 3 leads and slightly inverted in CS_5. The blood carbon-dioxide combining power was 7 mm. per liter on the first reading and rose rapidly. On the preceding day he had walked into another hospital in early acidosis. During the succeeding twelve hours he had been given 385 gm. of glucose parenterally and by mouth. Despite the administration of 230 units of insulin he had become entirely comatose, and the blood sugar had reached the level of 678 mg. An additional 220 units of insulin was required to reduce the blood-sugar level

TABLE 1. *Diabetic Coma in a Six-Year-Old Child.*

TIME	BLOOD SUGAR	BLOOD CARBON-DIOXIDE CONTENT	BLOOD NONPROTEIN NITROGEN	INSULIN	TREATMENT SALINE SOLUTION (PARENTERALLY)	FOOD (CARBOHYDRATE)
	mg./100 cc.	*mm./liter*	*mg.*	*units*	*cc.*	*gm.*
November 27, 1950						
10:00 a.m.	1060	7		120	1000	
12:00 noon	730			80		
4:00 p.m.	330	14	73	50	1000	
8:00 p.m.	103				1000	
Midnight to 7:00 a.m.						70
November 28	96					
November 29	256		23	14		
December 6	Discharge (Diet: C. 149, P. 61, F. 71. Insulin: 10 units of regular insulin and 22 units of NPH insulin.)					

The blood nonprotein nitrogen was 73 mg. at 4:00 p.m. but became normal in 2 days. The insulin dose of 200 units in the first 2 hours of treatment was supplemented by 50 units at the end of 6 hours. The total injected fluid amounted to 3000 cc. of physiologic salt solution.

The child did well within the next few days and was discharged home on December 6, on a regimen of 32 units of insulin with a diet of carbohydrate 149 gm., protein 61 gm. and fat 71 gm.

DISCUSSION

Factitious Insulin Resistance

Should this child have received glucose solution by vein? In 14 fatal cases of coma reviewed by Root[1] to 220 mg. Death occurred within a few hours. A post-mortem examination showed the liver cells well filled with glycogen. No complications that might have contributed to the fatality were found.

In a child described by Sindoni,[2] treatment was begun by the intravenous administration of 1000 cc. of 5 per cent glucose solution, and continuous administration of glucose solution was maintained. Within a twenty-four-hour period 4000 cc. of 5 per cent glucose in normal salt solution was given intravenously, as well as 800 cc. of 2½ per cent glucose

TABLE 2. *Uremia, Hyperkalemia and Juvenile Diabetes in a Thirty-One-Year-Old Patient with Diabetes for Nineteen Years.*

DATE	BLOOD					
	SUGAR	NONPROTEIN NITROGEN	CARBON-DIOXIDE CONTENT	CHLORIDES	SODIUM	POTASSIUM
	mg./100 cc.	*mg./100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
March 3, 1950						
9 p.m.	845		7			
11 p.m.	700		6	113	—	—
1 a.m.	470		7			
5 a.m.	181	100	8			
9 a.m.	51		8			
March 5	264	75	17	—	—	—
March 11	403	83	13	93	136	4.41
March 17	233	135	—	79	—	7.82

the parenteral administration of large amounts of glucose solution during the first few hours of the treatment of diabetic coma was followed by such catastrophes as the development of high degrees of insulin resistance, anuria and death.

An illustration of factitious insulin resistance is Case No. 23935, a 19-year-old boy admitted to the New England Deaconess Hospital in deep coma.[2] in water by hypodermoclysis. Seven thousand, two hundred and twenty units of insulin were given in 14 hours. Such treatment inevitably increases the amount of insulin required.

If one reviews the chemical reaction concerned in glucose utilization, one sees that the initial step is the phosphorylation of glucose by adenosinetriphosphate, a reaction catalyzed by hexokinase, to

yield glucose-6-PO_4. This hexose ester can then be converted to glucose-1-PO_4, and thence to glycogen in other enzymatic steps. Glucose-6-PO_4 may also be converted to fructose-6-PO_4 and thence to pyruvate via the glycolytic reactions of Embden and Meyerhof and the 3-carbon pyruvate finally oxidized to CO_2 and H_2O. Increasing evidence is accumulating to support the idea advanced by Cori[4] that insulin affects the phosphorylation of glucose by hexokinase. Presumably the hormone combines with hexokinase in some way to enhance its catalytic effect. In the absence of insulin all the reactions of glucose are slowed because of the chemical bottleneck at the first step in its utilization, a block that on theoretical grounds might be increased by a great excess of substrate.[5] The amount of insulin required to bring this reaction under control in the presence of excess substrate may become enormous, as is attested by clinical experience. Insulin also promotes the formation of fatty acids from glucose, perhaps by acting at another site. This additional pathway for utilization of sugar would also be obviated by blockage of the first step in glucose utilization, to the disadvantage of the patient. The large amount of insulin required is thus artificial and the condition is one of not genuine but merely factitious and apparent insulin resistance. Meyer and Salt[6] describe a case in which when glucose solution was given the blood sugar was raised to 2100 mg. and 660 units of insulin were required for the patient's recovery. Similar experiences have been reported many times.

The administration of glucose solution to a patient in diabetic coma who already has a high blood sugar increases the dehydrating effects of high molecular concentration in the extracellular fluid on the intracellular compartment. Glucose solution when administered does not enter the cells but by increasing the molecular and osmotic concentration in the extracellular fluid causes the withdrawal of water from the cells and thus controverts the very process of hydration for the intracellular mass that is sought as a major objective.

When large amounts of insulin are given in the presence of a high concentration of glucose in the blood, a rapid formation of glycogen naturally occurs. In the deposit of glycogen, potassium is withdrawn from the blood serum (Fenn[7]); therefore one of the major elements in serious hypokalemia may be the administration of glucose solution. A further objection to the use of glucose is that its administration makes impossible the use of the blood-sugar level as a guide in estimating the degree of insulin resistance and therefore the rapidity with which insulin must be used during the first five or six hours of treatment.

Hazards of Treatment

Three periods of great danger in the treatment of coma occur: on admission, when failure to give enough insulin in face of rapidly increasing insulin resistance may cause a fatal delay; after administration of large doses of insulin, when failure to watch the declining blood sugar may lead to giving excessive insulin; and after glucose and insulin administration, when hypokalemia may develop.

Case Report

Case 2 (9822). A 31-year-old woman was admitted on March 3, 1950, for treatment of "coma." One week before admission after local treatment and intramuscular injection of penicillin, an abscess in the buttock was surgically drained. For 2 days the urine output had been low. Vomiting had been followed by "deep breathing" and unconsciousness.

Diabetes was discovered in September, 1930, at the age of 11 years, after a 4-month period of weight loss, polyuria, polydipsia and polyphagia. In March, 1931, at the New England Deaconess Hospital, she was found to weigh 86 pounds and was 58 inches tall. At that time 12 units of crystalline insulin were started twice daily. Little is known about the control of her diabetes during the next 9 years. During this period she had three abscesses that required drainage. In 1943, at the age of 24, the patient returned because of edema. At this time she was taking 10 units of regular insulin and 20 units of protamine zinc insulin daily. She weighed 116 pounds. Several small retinal hemorrhages were seen. The blood pressure was 130/70. Examination of the urine revealed an albumin concentration of 250 mg. per 100 cc. and many leukocytes. The phenolsulfonphthalein excretion was 65 per cent in 2 hours. The nonprotein nitrogen was 41 mg. per 100 cc. Grade II calcification of the arteries about the ankles was shown by x-ray.

Table 2 (*Concluded*).

Date	Urine: Acetone bodies	Urine: Amount in 24 hours	Urine: Sugar	Urine: Albumin	Urine: Sediment	Insulin	Treatment fluids
	mg.	*cc.*	*gm./24 hr.*	*mg.*			
March 3, 1950 9 p.m.							5000 cc. N. Saline I.V.
11 p.m.	Less than 5	2800	—	740	Few W.B.C.	500	
5 a.m.							
9 a.m.							
March 5	—	2200	0	181	W.B.C. few R.B.C.	56	Routine
March 11	—	80	0.24	390	Packed W.B.C.	66	Routine
March 17	—	200	0	—	—	58	50 cc. 5% D/W with 30 units insulin I.V.

Marked Kussmaul respiration, drowsiness and dryness of the skin were noted. The eyeballs were soft and the tongue was dry. The rectal temperature was 98.4°F. The pulse was slow, the blood pressure 134/84 and the respirations 23. The stomach was dilated, and the bladder was distended to the umbilicus. A fluctuant and partially drained right ischiorectal abscess was present. On admission 1400 cc. of urine was obtained by catheterization, and tests for diacetic acid and sugar were both ++++. On aspiration the stomach was found to contain 300 cc. of brown liquid. Table 2 summarizes the patient's record. On admission the blood sugar was 845 mg. per 100 cc. and the plasma carbon-dioxide content 7 milliequiv. per liter. The patient received 500 units of crystalline insulin and 5000 cc. of normal saline solution in the first 6 hours. The nonprotein nitrogen was 100 mg. per 100 cc. Determination of total plasma acetone bodies was reported as less than 5 mg. per 100 cc., confirming the diagnosis of uremia rather than of ketosis. At the end of 2, 4, 8 and 12 hours the blood-sugar levels were 700, 470, 181 and 51 mg. per 100 cc. respectively. Restlessness continued. Only 350 cc. of urine was secreted, in spite of intravenous injection of 5000 cc. of normal saline solution in the first 12 hours. However, in the first 24 hours the output was 280 cc., and in the following 24 hours the urinary excretion was 2200 cc. Twenty-four hours after admission the patient was still breathing deeply and was quite drowsy, but she could be aroused. On the 5th hospital day the 24-hour urinary output fell to below 600 cc. The urine was found to contain 181 mg. per 100 cc. of albumin and many leukocytes. On one occasion the urine culture was positive for *E. coli*. She was given streptomycin, Gantrisin and Chloromycetin. After the 5th hospital day the urinary output was never adequate. She excreted only 80 cc. of urine on the 7th hospital day, when the serum sodium was 136 milliequiv. per liter, the serum potassium 4.41 milliequiv. per liter, the serum chloride 93 milliequiv. per liter and the serum phosphorus 10.2 mg. per 100 cc. On the 9th hospital day the nonprotein nitrogen was 123 mg. per 100 cc. On the 10th hospital day the serum calcium was 7.4 mg. per 100 cc. The plasma carbon-dioxide content at this time was 13 milliequiv. per liter. On the 11th hospital day, after intravenous injection of dextrose solution the patient developed acute pulmonary edema and pulsus paradoxus. She responded well to conventional treatment but on the 12th hospital day she began to breathe irregularly, with moderately long periods of apnea. She was very drowsy, and her tongue continually protruded from her mouth. She had peripheral edema, and her urinary output was practically nil. On the morning of the 13th hospital day her condition was essentially unchanged, but in the afternoon she became completely unconscious, with marked generalized hypotonia and absent tendon reflexes. Loud rhonchi were heard throughout the chest. The blood pressure was 78/60. An electrocardiogram suggested hyperkalemia. The serum potassium at this time was 7.82 milliequiv. per liter. Large quantities of viscous mucus made frequent aspiration of air passages necessary. Early on the 14th day the patient suddenly died.

Post-mortem examination showed the kidneys to be the seat of the disease chiefly responsible for death. Cerebral edema and petechial hemorrhages in the cortex, calcified coronary arteries and reduction in number of the Islands of Langerhans were also noted. Thickening of the capsule of the kidney and many foci of lymphocytic and plasma-cell infiltration were seen in the renal cortex. The glomerular caps were swollen and infiltrated by leukocytes, with adhesions of the tufts to the capsule in many. Hyalinization of the smaller arteries was noted, particularly marked in the arterioles, especially the afferent branches. The typical globular hyaline masses of intercapillary glomerulosclerosis were seen in the glomeruli. The kidneys showed typical diabetic nephropathy, characterized by marked arteriosclerosis, arteriolosclerosis (particularly of the afferent arterioles), intercapillary glomerulosclerosis, pyelonephritis and some lesions of glomerulonephritis.

Discussion

Intercapillary glomerulosclerosis, better known as diabetic nephropathy, has been observed at the New England Deaconess Hospital most frequently in patients whose diabetes had its onset early in life. Thus, in 43 patients exhibiting this renal complication, reported by Mann, Gardner, and Root,[8] the age at which this lesion most frequently developed was from twenty-five to thirty-five years, with previous diabetes for twelve to fifteen years.

Case 2 illustrates many features of this group. For nine months after the onset of diabetes at the age of eleven years, she received no insulin and lost 22 pounds in weight, or 1/5 her body weight. Her height for that age was normal. In the next five years she grew only 1½ inches, in contrast to the normal 8 inches of growth. Diabetic children are often superior in stature at the onset of diabetes, but many, treated inadequately, later fail to attain normal growth. Delay in the use of insulin, poor control of diabetes and consequent infections played significant roles in this patient. Malignant generalized vascular damage appeared, progressed and terminated life within seven years. Of all factors, good control of the diabetes proved most effective in preventing nephrosclerosis, arteriosclerosis and retinitis in 103 patients studied after twenty to thirty years of diabetes by Wilson, Root and Marble.[9]

Case 2 demonstrates the typical variety of kidney lesions seen in this juvenile group at the New England Deaconess Hospital. The glomerular lesion, emphasized by Kimmelstiel and Wilson[10] in 1936, was the rounded hyaline mass in the central portion of the glomerular lobules. However, lesser degrees of glomerular involvement with only focal fibrosis without hyalinization were described by Laipply and others.[11]

The original descriptions of the Kimmelstiel-Wilson lesion emphasized the mild character of the diabetes and its occurrence chiefly in middle and late life. The lesions are actually more frequent and fatal in young persons with severe diabetes of long duration. Of 135 fatal childhood cases of diabetes, Joslin and Wilson[12] reported that over 50 per cent of the deaths were due to this diabetic nephropathy. White and Waskow[13] found that all juvenile diabetics who died after 1940 having had diabetes for fifteen years or more showed intercapillary glomerulosclerosis. In contrast, the development of this typical fatal renal failure among diabetics in middle and late life is much less common.[14-19] In discussions of this problem, the mildness of the diabetes has repeatedly been stressed. Indeed, Rifkin[17] points out that "the diabetes may be so mild as to escape detection until specifically searched for by means of the glucose tolerance test." This applies to older patients. Juvenile diabetes is severe; therefore its greater frequency in the young patients after fifteen years of diabetes supports the theory that the lesion is essentially related to severe and uncontrolled diabetes. A confusing fact is that in this youthful group, as the renal lesion advances and nitrogen retention develops, a striking diminution in the insulin requirement may lead

to an erroneous evaluation of the severity of the diabetes. Toward the end of life such youthful patients may be taking little or no insulin. Whatever the explanation for this decline in the insulin requirement (malnutrition, loss of appetite, vomiting), it makes the diabetes appear mild, whereas in reality the renal lesion develops at a time when diabetes is most severe. This problem, then, is not one of advancing age but predominantly of long continued, severe diabetes under inadequate control. At present the only cases of childhood and youthful diabetes in which the patient has survived twenty-five years of the disease without clinical evidence of diabetic nephrosclerosis are those in which the diabetes has been well controlled by early and continued use of insulin, proper diet and close medical supervision.

Case 2 presented a problem in differential diagnosis between uremia and diabetic coma. Development of an ischiorectal abscess was followed by vomiting, fever, drowsiness and air hunger. Generalized dehydration, soft eyeballs, Kussmaul breathing, glycosuria, hyperglycemia and ketonuria suggested true diabetic coma. The carbon-dioxide content of 8 milliequiv. per liter was consistent with acidosis due to either uremia or diabetic coma. Only the chemical demonstration of the absence of any abnormal increase in ketone bodies in the blood eliminated diabetic coma. The blood nonprotein nitrogen of 100 mg. per 100 cc. established the diagnosis of uremia. The qualitative test for acetone in the blood plasma is a valuable aid in the rapid diagnosis of ketosis.

Changes in the plasma potassium may be expected with failing renal function.[20-24] In Case 2 three factors favoring hyperkalemia had been present: inadequate renal excretion of potassium, increased protein catabolism with transfer of cell potassium to the extracellular compartment and dehydration with contraction of the volume of extracellular fluid.

The toxic effects on the heart of increased concentrations of potassium in blood serum have been repeatedly studied since Blake's first demonstration in 1839 on the heart of dogs. Since 1938 many reports of the effects of hyperkalemia on the electrocardiogram have appeared.[21, 23-24] Tarail[23] found that electrocardiographic disturbances were constantly present when the serum potassium was above 7.8 milliequiv. per liter. The serum potassium was 7.82 milliequiv. per liter in Case 2. The most characteristic changes of hyperkalemia are heightening and peaking of the T waves, intraventricular block, auriculoventricular block, sinoauricular arrest, auricular standstill, idioventricular rhythm and the chaotic rhythm of *cor mortuum*.[28] The patient here reported exhibited the following: partial auriculoventricular block, intraventricular block and marked heightening of the T waves. Finch and others[30] reported that the P waves disappeared before spreading of the QRS complex occurred. The treatment of hyperkalemia may be unsatisfactory when the condition is due to uremia. However, the reversal of hyperkalemia is possible and lifesaving at times — namely, after prolonged and excessive oral administration of potassium to patients with mild renal disease, in the crisis of Addison's disease and in the crush syndrome. Intraventricular block may occasionally be reversed when the renal lesion is reversible or mild in nature. Most authors agree that sodium chloride and calcium should be administered. The intravenous administration of sodium chloride may cause a reversal of the electrocardiographic changes and a return of muscle function, with or without a decline in the serum potassium level. The administration of glucose and insulin simultaneously to combat hyperkalemia may be efficacious,[25] as was suggested by Bywaters[26] in the treatment of the hyperkalemia following ischemic muscle necrosis, and as carried out by Elkinton, Tarail and Peters[20] in 2 cases. Finally, potassium is bound to cellular protein, and because testosterone administration favors protein anabolism it is theoretically possible to give testosterone to lower the blood potassium level. In general, however, hyperkalemia caused by severe renal disease with anuria is not significantly influenced by any of these measures.

Summary

Uncomplicated diabetic coma, occurring at the discovery of diabetes in a child, and uremic coma as a late complication of childhood diabetes are described.

Factitious insulin resistance may result when glucose is injected at the height of diabetic coma before insulin actually becomes effective.

The pathology of diabetic nephropathy in juvenile diabetes of long duration includes Kimmelstiel-Wilson lesions in the glomeruli, chronic pyelonephritis, marked arteriolosclerosis and generalized arteriosclerosis.

Uremic acidosis simulated diabetic coma in the presence of soft eyeballs, dehydration, hyperglycemia and typical air hunger but was differentiated by the demonstration of the lack of increased ketone bodies in the blood.

Fatal hyperkalemia with marked electrocardiographic changes occurred in a patient with uremic acidosis, although no potassium solution had been administered.

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MEDICAL PROGRESS

CEREBRAL PALSY (Concluded)

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PSYCHOLOGY

During the past five years a growing interest has been shown in the psychologic appraisal of patients with cerebral palsy. Psychologic studies include intellectual evaluation, projective technics and experiments in perception and conceptual thinking.

Intellectual Evaluation

The incidence of mental deficiency in cerebral palsy has been estimated differently by various authors. McIntire[123] has reported an incidence of mental deficiency of 18 per cent; Phelps[124] reports an incidence of 28 per cent; and other authors have found mental deficiency in 45 to 50 per cent of their cases.[125, 126] Thus it appears that retardation in children with cerebral palsy may be greater than previously estimated. Recent studies report no significant difference in distribution of intelligence among spastics, athetoids and ataxics.[127] Median intelligence quotients of 75 have been found for groups of children with cerebral palsy, but athetoids seem to have a higher mean intelligence quotient than spastics.[126, 128]

McIntire[129] found that the incidence of mental deficiency was approximately twice as great in spastic hemiplegia on the right side as in that on the left, and over twice as great in right-sided as in left-sided spastic quadriplegia. These studies definitely raise the question of the importance of the localization of the cerebral damage and of differences in different types of cerebral palsy.

Limited environmental opportunities and learning experiences have been postulated as contributing causes of the mental retardation found in so many cerebral-palsy patients.[89, 130, 131] However, when a group of such children were tested before and after extensive periods (fourteen to seventy-six months) of physical, occupational and speech therapy, academic instruction and social contacts in a group, it was found that only one child showed an increase of 10 I. Q. points.[132]

New Technics in Testing

The most common tests currently used in the intellectual evaluation of cerebral-palsy patients are the Revised Stanford-Binet, the Wechsler Intelli-

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gence Scale for Children, the Goodenough Draw-A-Man Test and the Bender Visual-Motor Gestalt Test. Numerous psychologists and other workers[124-125, 130] have emphasized the inadequacies of present tests for evaluating the intellectual potential of cerebral-palsy patients. However, Bice[133] believes that the flexible use of current tests is justified. Strother[134] and Holden[135] have emphasized that the child's range of abilities in different intellectual areas (perception, conceptual thinking, vocabulary, memory, motor skills) is more important than a simple intelligence quotient.

Two new tests have been reported that are thought to have possibilities of more accurate evaluation. Tracht[127] discusses Raven's Progressive Matrices Test, which consists of 60 different and progressively more difficult patterns or matrices. Each picture pattern has a section missing, and the subject must choose the correct part to complete the pattern. No language or fine muscular co-ordination is required. The application of this test to children with brain injuries has been criticized[135] because it is based on visual form perception, a faculty that is often seriously impaired in persons with brain damage.

Another new intelligence test that may prove useful is the Ammons Full Range Picture Vocabulary Test,[136] which consists of 64 drawings, 4 to a card. The subject's task is to point to the picture on each card that best represents the meaning of a word given verbally by the examiner. Since the test can be used from kindergarten to adult levels, it is valuable in some cases, as no speech and only minimal motor performance is required of the subject.

In attempting to use psychologic tests as aids in differential diagnosis, Sarason and Sarason[137] classified defective children with cerebral palsy into two groups: those in whom cerebral disease was probably the primary cause of the mental deficiency and those cases in which it was not. Electroencephalographic records showed abnormalities in 75 per cent of the first group and in only 22 per cent of the second group.

Projective Technics

Projective technics such as the Rorschach test, the Thematic Apperception Test and the Goodenough Draw-A-Man test have been used for appraisal of emotional problems in children with cerebral palsy. Machover[138] has shown that children frequently project disturbances of body image and motor disabilities in their drawings. Special projective technics such as Bachrach's modified Thematic Apperception Test cards, especially drawn for crippled children, have been used recently.[139]

Portenier[140] found emotional immaturity as characteristic of children with cerebral palsy, as well as lack of persistence, lack of adequate socialization and fatigability. Tracht[141] gave Guilford's Inventory of Factors to adults with cerebral palsy; these subjects showed greater introversion, more depression and less emotional stability than a normal control group. Phelps[142] states that spastics seem seclusive and athetoids are outgoing. However, other authors do not confirm this sharp psychologic differentiation.[114]

Thus far the only reported individual personality study of children with cerebral palsy is a study by Klapper and Werner[143] of the members with brain damage of three pairs of identical twins. The spastic member of two pairs showed perseveration, perceptual impairment, immature conceptualization, difficulty in abstracting, distractibility and body-image disturbance. The third twin, diagnosed as "cerebral palsy with tremor," was found no different from his twin in intelligence or perception but showed somewhat inferior conceptual thinking.

Perception and Conceptual Thinking

Experimental studies concerned with perception and conceptual thinking have been adequately summarized by Strauss and Lehtinen.[5]

Meyer[144] has recently indicated that spastics tend to be poor in concept formation and perception but relatively good in auditory acuity and verbal fluency, whereas athetoids tend to be poor in speech but good in concept formation and comprehension. This again raises the basic question of the adequacy of classifying all cerebral palsies as if they were similar, a point made recently by Bice.[133]

Probably one important deterrent to more productive psychologic experimentation has been the lack of an explicit theoretical framework. Goldstein's concepts of the results of brain injury,[145] such as loss of categorical behavior and the "catastrophic reaction," have been stimulating to some extent, but his theory has not as yet been systematically tested in cerebral-palsy patients.

Habilitation

The current use of the term "habilitation" rather than "treatment" implies the recognition of the need to equip the cerebral-palsy patient with the means of developing his fullest potentialities.[146] This requires the use of a multitude of physical, educational and recreational resources, as well as proper handling of the emotional aspects of physical handicaps.[147] It is hoped that this over-all therapeutic approach will help to alleviate the current major problem of cerebral palsy. This problem concerns adults who are unable to be integrated into, or are unacceptable to, the community, after spending years in braces, casts and rigid training preparing themselves for a place in society.

Motor Re-Education

The aims of motor re-education are to secure muscular relaxation, train voluntary muscular control and build proper developmental patterns into useful activities.[6] These goals are usually achieved through the various therapies, with the help of

orthopedic, neurosurgical and pharmacologic measures. The alleviation of hearing, visual, psychiatric and dental problems contributes to the program.

Orthopedic

Orthopedic treatment is aimed at helping the patient to achieve functional mobility and improve his appearance.[148] Physical therapy and a variety of mechanical aids for sitting, standing, walking and functional use of the arms and hands are utilized to achieve this goal.

Braces are used to prevent and correct deformities, to support, to control voluntary motions, to assist in wanted motion and occasionally to predetermine the effect of surgical arthrodesis of a joint.[149] The two types of braces most used in cerebral palsy are corrective and control braces. The control brace is most often applied to control unnecessary movement in athetoids and scissors gait in spastics. The corrective brace is utilized to correct deformities resulting from, but actually not part of, cerebral palsy.[150]

Phelps has pointed out the futility of heel-cord tenotomy until full bone growth has occurred. Instead, night braces worn through adolescence will prevent contracture and permit a normal gait.[150] Craig recommends correcting the equinus deformity by stretching and the use of wedged plaster boots.[148]

Surgery is utilized only to surmount some definite obstacle to progress. Chandler[151] believes that the greatest benefit is derived from correction of the scissors gait in spastics. Spasm of the adductor group is greatly reduced by neurectomy; fixed contractors can be corrected by tenotomy or myotomy at the origins of the adductor group. Correction of full-flexion deformities by myotomy of the hamstrings or neurectomy of the sciatic branches supplying the hamstring group is often indicated. In properly selected cases, patellar advancement will permit complete active extension of the knee.

Carrol and Craig[148] outline several worth-while surgical technics. They point out the different functional aims in surgery of the upper and lower extremities. In the upper extremity, there are procedures that help to overcome flexion deformities of the wrist and elbow, adduction of the thumb into the palm (either singly or as a tight fist), flexion of digits into the palm and pronation of the forearm. In the lower extremities, operative technics are of greatest value in the spastic child and are of limited or of no value in athetosis, tremors, ataxia or rigidity. These workers discuss methods involving correction of the foot, knee and hip. They also point out that the handling of fractures in cerebral palsy frequently requires special precautions due to the abnormal neuromuscular status.

Neurosurgery

Neurosurgical treatment may become increasingly valuable in the control of muscular overflow resulting from extrapyramidal disorders. Putnam[9] considers the operative treatment of athetosis and dystonia by resection of Area 6 or by section of the extrapyramidal pathways in the anterior column of the spinal cord deserving of more attention, even though the results are far from perfect. He also discusses operation for the treatment of alternating tremor, rigidity and ataxia. Myers expresses hope that neurosurgical treatment of extrapyramidal areas may eventually be the answer to current problems on this disorder.[152]

Athetosis, tremor and chorea can be abolished by extirpation of the precentral gyrus. However, paralysis of the affected limb results. It has been reported that removal of the frontal cortex anterior to the precentral gyrus stops involuntary movements without causing paralysis, but confirmation has not been forthcoming.[153] Successful results have been reported in 10 of 12 patients with infantile hemiplegia treated by removal of one cerebral hemisphere.[154] Improvements in hemiplegia have also been reported after treatment by subcortical sections[155] and cortical excisions.[156] One must await confirmation of the efficacy of these drastic operations before regarding them enthusiastically.

Revascularization

Attempts have been made to increase cerebral blood supply by means of a cervical arteriovenous fistula. In general, patients selected for the operation have been those with cerebral palsy, mental retardation and convulsive disorders. Twenty-six per cent of the children with cerebral palsy demonstrated decreased muscle tone with or without improved motor function. Final conclusions are still pending.[25, 157] The chief objection to the operation is that there is no proof that it increases oxygenation of the cerebral tissues, and it may have many dangerous sequelae.[158]

Drug Therapy

Drugs that have a specific controlling action in abnormal neuromotor conditions have been a hoped-for panacea in cerebral palsy. Thus far a wide variety of pharmacologic preparations have failed to fulfill the functions expected from such medications. Ideally, these should have a constant beneficial effect on spasticity and involuntary motion without impairing voluntary motion; should have a favorable effect on the behavioral or emotional status; and should be nontoxic.[159] New methods for studying drug action, particularly in relation to the neuromotor system, promise rational approaches in the pharmacologic aspects of abnormal muscular states and movements.[160, 161]

Neostigmine. The enthusiasm for the use of neostigmine bromide (prostigmine bromide) in cerebral palsy has dwindled, and current reports have not confirmed those of the original investigators.[162] Perlstein and Barnett[163] demonstrated the impor-

tance of suggestion when a popularized drug is used. They obtained improvement in even severe cases of cerebral palsy with a placebo replacing neostigmine. This emphasizes that improvement must be carefully assessed before it should be attributed to any single measure.

Drugs with curariform action (curare and curare-like derivatives). The clinical use of curare is based on its ability to create a transient block at the myoneural junctions. Purified natural preparations of uniform potency such as *Chondrodendron tomentosum* extract (Intocostrin), d-tubocurarine chloride, dimethyltubocurarine, and a large number of synthetic compounds such as decamethonium (decamethylene 1,10-bis trimethylammonium), syncurine, or C10, and 1, 2, 3-tri (diethylaminoethoxy) benzenetriethyl iodide (flaxedil) are now available commercially. These all differ characteristically from each other in potency, duration of action and effect on respiration.[161] Schlesinger[164] believes that these drugs are useful in the treatment of spasticity through their reduction of abnormal neuromuscular patterns. However, they are not meant as a substitute for other measures of habilitation. Other authors have reported curare to be of little use in treatment.[165, 166] The disadvantages of curare and its derivatives are its extreme paralyzing action, the small threshold between a toxic and a lethal dose and its ineffectiveness when taken orally. Mephenesin (3-ortho-toloxyl-1, 2, propanediol) (tolserol) is a synthetic chemical compound with a curare-like action. Its chief site of activity is believed to be in the brain stem at the level of the thalamus and below.[167] Reports vary from dramatic relief in spasticity and moderate relief in tremor and rigidity[168] to negligible amelioration of these conditions.[169, 169, 170] In general, with oral dosage the drug diminishes the overactive responses of superficial and deep reflexes, has an inconsistent effect on diminishing overflow, and in some children favorably alters behavior.[171, 172] Toxic effects in therapeutic doses are not uncommon and generally consist of gastric upsets, listlessness and weakness.[159] Leukopenia and anemia have been reported.[173] Prenderol (2, 2-diethyl 1, 3-propanediol), is one of a group of drugs chemically related to mephenesin. It has a higher anticonvulsant action than mephenesin, but is a less potent paralyzing agent. In animals it has little effect on the normal knee jerk but depresses flexion and crossed-extension reflexes. These findings have been considered evidence consistent with a selective depression of multisynaptic neurone arcs in the spinal cord.[174] It is administered orally in doses varying from 45 to 150 mg. per pound of body weight per twenty-four hours. In preliminary clinical trial in children with cerebral palsy, it has been found to depress reflexes more consistently than mephenesin, and less toxic reactions are reported.[175]

Anticonvulsants. Anticonvulsant drugs, possibly except for Tridione, do not improve the neuromuscular status. Perlstein and Andelman[176] found that Tridione seemed beneficial in relieving voluntary tension in athetosis but was of little value in spasticity or dystonia. Denker and Kaplan[177] could not confirm this observation. Since convulsive seizures are so common in cerebral palsy, a knowledge of anticonvulsant drug therapy is essential for the proper treatment of these cases.[178]

Amphetamines. l and r amphetamine sulfates in daily doses of from 5 to 40 mg. not infrequently have a beneficial effect, quieting or improving concentration in children with personality disorders resulting from brain damage.[110]

Glutamic acid. Glutamic acid, in daily doses as large as 12 gm., has been recommended to improve learning ability in children with convulsions or retardation.[179] The beneficial effects reported have not been confirmed.[180, 181]

Physical Therapy

Specific physiotherapeutic technics used in neuromuscular training have been outlined.[6, 8] Schwartz and his co-workers,[3] having had disappointing results with the traditional passive physical therapy and bracing, evolved special motivating devices that measurably improve the child's manipulative potential over gravity. The outstanding example is the Hartwell Carrier, a motor-driven overhead suspension carrier that has enabled the cerebral-palsy patient to learn the pattern of walking more quickly. The successes that the child achieves through this device encourage increasingly complex activities that lead to physical independence.

Occupational Therapy

One of the foremost aims of occupational therapy has been the stressing of self-help activities.[6, 182, 183] Included in these are dressing, self-feeding skills and toilet activities. As a preliminary to mastering these skills, the use of toys[184] has been found to be of great importance. The development of co-ordination in hand skill is a slow and laborious undertaking, and much depends on the intelligent selection of play material. Many of the toys designed for the normal child can be used by the child with cerebral palsy with minor adaptations. Special toys may need to be constructed to provide the necessary patterns for self-help activities.

The occupational therapist frequently faces the problem of the child whose handedness is undetermined because brain damage has disturbed normal dominance. Training of the wrong hand may result in difficulties of speech and emotional adjustment. A handedness-determination test has been described.[185, 186]

Eyedness should be tested and should be considered in deciding which hand is to be trained.

In the majority of cases the dominant eye is on the side corresponding with the dominant hand.[186]

Special Problems

Ophthalmology

Guibor[187] reviewed the ophthalmologic problems in cerebral palsy. He estimates that between 40 and 50 per cent of such patients have strabismus, as compared to an incidence of 2 per cent of the normal population. Discussions of the ocular neurophysiology and pathology of cerebral palsy are available, as well as classifications of associated ocular movements.[187-189] Conjugate ocular deviations are most common; they are frequently associated with nystagmus. Nystagmus of wide amplitude is often found in athetoid patients, as well as amblyopia. Nonsurgical treatment of the strabismus with atropine, glasses and prism lenses improves the vision and ocular co-ordination when contractures of the ocular muscles are absent. Surgical treatment of those with athetosis is usually unsuccessful in removing the strabismus. Early treatment of these motor defects will not only conserve vision but improve co-ordination of the extremities.[190]

Hearing Disorders

Aside from the hearing disabilities found in athetotic and labyrinthine ataxic groups, it has been generally believed that there is little direct association between cerebral palsy and impaired hearing. However, Hardy[191] has found a variety of nerve-type hearing lesions in children with all types of cerebral palsy; comparable to that of children who are normal except for hearing difficulties. Characteristics of nerve deafness are greater loss of acuity for the high tones than for the low tones and considerable distortion of speech hearing. Although relatively few children with this disability are totally deaf, the partial deafness must be considered an additional handicap in cerebral palsy, since these losses have been shown to interfere with learning patterns.[192]

There is increasing evidence to suggest that many of the causes of cerebral palsy also produce hearing impairment. There is also some evidence to suggest that the auditory defect associated with isoimmunization disorders (in children) lies in the auditory nuclei rather than in the cochlea.[193] These findings warrant further investigation and may shed light on the reasons for the similarity of audiograms of children with a history of erythroblastosis and audiograms of children with deafness due to other causes, such as prenatal rubella.[191]

A common cause of hearing loss in cerebral palsy is the presence of impacted cerumen in the external auditory meatus. With removal there may be immediate auditory response.[192]

The treatment of hearing loss revolves around the teaching of speech reading, the proper use of hearing aids and the integration of basic psychologic principles into the training program.

Hearing Tests

Present methods of evaluating hearing loss in children leave much to be desired. The difficulties in testing children with cerebral palsy are obviously even greater than those of testing normal children. Jones,[194] in a critical review, points out the errors due to human and mechanical elements in both pure-tone and speech audiometry. Various mechanical instruments have been devised, such as a vibrating buzzer[195] and a "peep show," to measure auditory acuity in children. A new instrument has been developed to give a highly sensitive record of galvanic skin-resistance response; it is designed to test the hearing threshold of infants and young children.[197] Studies made by this means have been enlarged to include children with cerebral palsy. There is little evidence that the curve of the audiogram is of particular diagnostic significance in cerebral palsy, children with cerebral palsy have audiograms that are characteristic of nerve deafness.[191]

Another evidence of progress in this difficult field is the successful use of the electroencephalogram in hearing evaluation. A comparison of sleeping and waking records after the sleeping infant has been stimulated by a noise can be utilized to demonstrate hearing ability.[198]

Speech Disorders

A majority of children with cerebral palsy have speech or voice disorders. No one type of speech characterizes cerebral palsy; these children are subject to the same speech disturbances found in other children[199, 200] — although probably in higher incidence.[192] However, most common are motor disturbances, which generally parallel the motor dysfunction of the extremities. Spasticity produces losses in reciprocal inhibition of the sucking process, laryngeal valves, breathing and so forth. Athetotic and choreiform movements of the tongue and larynx are frequent in extrapyramidal disorders, and synergistic patterns are distorted in lesions of the cerebellum.[192]

Aphasic signs are frequently associated with the motor disturbance, and in children it is often hard to determine whether dysarthria exists exclusively or concomitantly with a certain degree of cortical motor aphasia.[200-202] Evaluation of mental ability must be included in this problem of differentiation, as aphasic children may appear feebleminded, although their intellectual levels are often higher.[202] At present, evidence indicates that the presence of brain damage does not obviate the subsequent development of language even in the presence of initial psychologic evidence suggestive of retardation.[70, 192, 202] Speech ability depends on the degree of relaxation of the muscles involved in speech pro-

duction, as well as motor and emotional relaxation in general.[204] Cass[148] outlines in detail the methods used in speech habilitation. Westlake[205] emphasizes that lack of speech in preschool children with cerebral palsy may be due to lack of interest or ability. A wide variety of everyday experiences are utilized to stimulate the child for speech readiness.

Dentistry

The dental problems of cerebral palsy are now being recognized, and methods of treatment are being explored. The major diseases and deformities are dental caries, inflammation and hypertrophy of the gingivae, destruction due to grinding, deformities of the arches and malocclusions resulting from abnormal musculature. The proper office approach and treatment technics have been thoroughly discussed.[206, 207]

Special Education

It has been emphasized that the child with cerebral palsy should be treated as nearly like a normal child as possible, although his education requires special attention. McIntire[208] studied the educational achievements of 500 such children; he found that 80 per cent were retarded one grade or more and that many were placed in classes beyond their abilities. The education of a number of these children was handicapped by speech, hearing and handedness disorders. Because of these disabilities, as well as disorders of perception, concept formation and behavior, educational methods must be geared to their particular mental organization. Strauss and Lehtinen[5, 209] outline technics for teaching fundamentals such as arithmetic, reading and writing to children with brain damage.

The severely handicapped child may benefit most from institutional or custodial care when the family can accept such a decision. The mildly or moderately handicapped may be integrated into the community provided that their disabilities are so alleviated that society's prejudice against the handicap is overcome.

Nursery School

The therapeutic nursery school has only recently been included in the program for cerebral palsied children. It serves as the medium within which physical, occupational and speech therapy can be given to the child. Intelligent aid from the parents is essential if the nursery school is to achieve its aim.[210-212]

General Outlook for Cerebral-Palsy Patients

The future of the child with cerebral palsy does not appear as gloomy as it did ten years ago, due to recent rapid advances. The prevention and improved treatment of some of the common diseases of pregnancy, the improvement in obstetrical technics and the more careful supervision of the premature and full-term newborn appear helpful in decreasing the number and severity of the cerebral-palsy cases caused by these factors. However, it must be emphasized that for the most part present information concerning all phases of cerebral palsy is incomplete and confusing, as many clinical observations are difficult to explain when subjected to analytic study. Nevertheless, the integrated approach through which the child's entire range of motor, sensory and emotional handicaps, rather than specific, isolated dysfunctions, is considered, is speeding the way to habilitation.

The social future of these children is difficult to predict, as so much depends on acceptance by the community. One thing is certain: If they are to be accepted, a distinction must be made (for the present at least) between children with mild motor handicaps and intelligence quotients above 80 and children with severe motor handicaps or mental deficiency or both. The first group requires a total effort by the therapeutic team, as these patients can be habilitated even though the process is slow. The advantages of training centers versus home treatment have recently been discussed.[213, 214] In general, this group should receive educational opportunities as nearly as possible similar to those of the normal child. Children classified in Group 2, particularly if they are diagnosed as mentally deficient, should be excluded from the long and expensive habilitation program because they lack the two essential factors of understanding and motivation. As has been pointed out above, there are difficulties of psychologic evaluation, and if the slightest doubt exists that the mental age obtained is not maximal re-evaluation is essential. However, once the mental deficiency has been established the only realistic measure is either home treatment or institutionalization.

The child with brain damage who has sensory impairment and perceptual difficulties presents the greatest habilitation challenge today. The almost complete lack of properly indoctrinated workers in this special educational field makes it impossible to ascertain the extent to which these children can profit from individualized methods of instruction.

For those patients in whom social adjustment may be expected, special educational facilities are becoming available.[215] Approximately 50 per cent of the medical schools in the United States already have departments of physical medicine and rehabilitation.[216] Special jobs, sheltered workshops and integration into normal economic life are now being emphasized.[217, 218] In a recent survey of adult cerebral-palsy patients made in Schenectady, New York, Levin and his co-workers[219] found that 21 per cent had full-time jobs, 17 per cent had part-time jobs and 62 per cent were not employed. It has been estimated that 55 per cent of patients with cerebral palsy can be enabled to earn their living in adulthood if their treatment and training are begun early in life and continued as long as necessary.[220]

Watkins[221] has pointed out that whereas the cost to society of care for the permanently disabled paraplegic is $25,000 to $50,000, the average cost of medical care and rehabilitation for such a patient is only $7500. Thus rehabilitation is not only a necessity from the humane point of view but an economic measure indispensable to the community.

Conclusions

Out of the vast amount of information summarized in this paper, the objectives of the treatment of cerebral palsy can be stated. They are:

Medically, to help the child to attain freedom of motion, communication and self-care.

Socially, to give the child experiences common to most children, to provide an opportunity to play at his own developmental level and to permit the child to do things for himself.

Emotionally, for the child to feel loved and wanted as a member of the family and of groups outside the family; to be recognized for achievements; and to have and maintain a place of his own.

For parents, to know that they are not alone, to have supportive friendships and to obtain factual understanding about the disabilities, limitations and potentialities of their child.

This co-ordinated approach to the child is best accomplished by a team under medical supervision. Such a program is attempted at the Meeting Street School, Cerebral Palsy Center.[212]

Summary

Cerebral palsy should be regarded as part of the brain-damage syndrome rather than as a separate disease entity.

Changing concepts resulting from researches related to the central nervous system are being utilized to clarify the problems of cerebral palsy.

Early diagnosis of cerebral palsy is possible when the developmental aspects are assayed at regular intervals and supplemental diagnostic technics are properly utilized.

Habilitation depends on a holistic approach; it should include the proper utilization of medical corrective technics, various modalities in physical, occupational and speech therapy and integration of special education and play into the total scheme. An understanding of the emotional handicaps of cerebral-palsy patients and their parents in combination with proper psychiatric guidance is an essential part of therapy.

The role of mental retardation in cerebral palsy is being clarified by improved psychologic testing methods and better understanding of the sensory and behavioral handicaps of the child with brain damage.

Cerebral palsy, in addition to being an important medical problem, has various nonmedical aspects, such as vocational guidance, education and employment.

The aim of treatment of cerebral palsy is to integrate as many as possible of these patients into society and to help them to live within their limitations.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 37461

PRESENTATION OF CASE

A seventy-five-year-old man entered the hospital because of pain in the left abdomen and lower back.

The day prior to admission he noted the onset of a steady ache in the left lower quadrant that gradually spread to the left lumbar area. This was made worse by moving and was relieved slightly by lying still. He vomited once. His physician thought he was able to palpate a pulsating mass in the left upper quadrant. There had been no change in bowel habit nor any bloody or tarry stools. There was no frequency, dysuria or other urinary symptoms.

Thirty years before admission he was told that he had "heart trouble." Thirty-five years prior to entry he had "nephritis" following an upper-respiratory infection, but there were no known sequelae. For many years he had had right-lower-back pain that was relieved by sacroiliac manipulation. He had never had pain in the left lower back.

Physical examination revealed a man in no distress. The heart was enlarged and aortic systolic and aortic diastolic murmurs were heard (these same murmurs had been present unchanged for many years). The left side of the abdomen was tense and full and at least one observer thought that there was slight pulsation in the area. The liver edge was palpated two fingerbreadths below the costal margin. No other organs and no masses could be palpated. Strong pedal pulsations were present. A moderately enlarged prostate was smooth, non-nodular and nontender. Reflexes in the knee were present; those in the ankle were equivocal.

The temperature was normal and the pulse 85. The blood pressure was 180 systolic, 90 diastolic.

Urinalysis showed a specific gravity of 1.024 and gave a + test for albumin; there was an occasional red and white cell and an occasional granular and hyaline cast in the sediment. Urine cultures and smears from the bladder and left kidney were negative for growth of organisms. Examination of the blood disclosed a hemoglobin of 10.5 gm., a red-cell count of 3,630,000, normal platelets and a white-cell count of 12,900, with 86 per cent neutrophils. A stool was guaiac negative. The nonprotein nitrogen was 38 mg. per 100 cc. A sedimentation rate was 61 mm. in one hour. The prothrombin time was normal. An electrocardiogram showed well marked left-axis deviation. X-ray films of the chest demonstrated enlargement of the left ventricle and an extremely tortuous and calcified aorta. An abdominal film showed normal sacroiliac and hip joints. The right kidney appeared grossly normal but the left kidney was not outlined and there was a suggestion of fullness just above the left iliac crest. There was no definite area of calcification in the abdomen. Intravenous pyelograms revealed a normal right kidney; the left was either enlarged or displaced somewhat laterally. An ill-defined soft-tissue mass about 10 cm. in its greatest diameter overlay the lower pole of the left kidney and psoas shadow. Both kidneys excreted contrast substance in diminished concentration. The right urinary passages were not grossly remarkable. On the left an arcuate density that apparently represented the pelves and upper ureter was present to the left of the second lumbar interspace. Retrograde pyelograms showed good filling of the left urinary passages. The calyces were not remarkable. The kidney appeared displaced slightly laterally and considerably anteriorly. The pelves and upper ureter were displaced upward and medially respectively. The line of the pelvis and ureter outlined a rather rounded shadow (Fig. 1). A barium-enema examination showed multiple diverticula but no evidence of intrinsic involvement of the colon. The descending colon just above the iliac crest was displaced outward by the mass.

The day following admission the left-lower-back pain had subsided considerably without therapy and the patient was ambulatory, complaining only of some weakness without much pain. The abdomen was soft and moderately distended. Just below the margin of the ribs on the left there was an area that was tender and tense. It was not possible to outline the boundaries of this area. For the next few days his condition remained unchanged, there being only slight discomfort and no change in the physical findings. The temperature varied between 99 and 100°F. The white-cell count on the fourth day was 20,200, with 77 per cent neutrophils.

On the tenth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GEORGE GILBERT SMITH*: "A moderately enlarged prostate was smooth, nontender and non-nodular." This does not say whether it was soft or

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hard. I do not think this statement is of any importance here, but I want to call attention to the frequently expressed idea that a malignant prostate must be nodular. The diagnosis of carcinoma should be made before the prostate reaches a nodular stage, that is, before there are definite nodules on the surface of the gland. A certain irregularity in the consistence of the gland is important.

Will you show the x-ray films now, please?

DR. STANLEY M. WYMAN: The enlarged left ventricle and the tortuous calcified aorta are well seen in the films of the chest. There is no evidence of active disease. The single film of the abdomen taken at the time of entry shows normal shadows of the liver, the right kidney and the spleen. The left kidney is poorly outlined and there seems to be an unusual soft-tissue mass in the left flank just above the iliac crest. The margins of it cannot be well defined, largely because of a considerable amount of gas in the bowel. Two days later more films again show the right kidney quite well outlined and the left kidney replaced by a soft-tissue mass extending down just above the iliac crest. The left kidney cannot be outlined separately from this shadow. After introduction of contrast substance the right urinary passages appear normal. On the left the upper calyces are quite well seen and are lying more laterally than usual. The arcuate density described appears to represent the pelvis and upper ureter displaced upward, and the soft-tissue fullness is continuous in the area below this. This was a constant finding on several films. It is confirmed by retrograde examination showing something lying on this region somewhat posteriorly and inferiorly to the kidney and inseparable from the shadow of the kidney (Fig. 1). There is no evidence of calcification in this mass. There is no evidence of invasion of the pelvis or calyces.

DR. SMITH: This is the history of a seventy-five-year-old arteriosclerotic man who had a sudden dull ache, so far as I know unprovoked by any factor such as trauma, sudden effort or a fall. When I say "sudden" I mean it apparently appeared within one day — it was not instantaneous. That dull ache began in the left lower quadrant, worked up into the left lumbar region and within forty-eight hours had largely disappeared. In its early phase it shifted and it was not at all like the pain that one would expect from a condition that had been going on for quite a long time — such as a renal tumor or cyst. Renal cysts are not likely to cause much pain, but a renal tumor of an advanced degree may involve the lumbar muscles and may cause pain of this general type.

What other facts do I find in going over this record besides the sudden development of ache in the left lower quadrant? This patient also had anemia, fever, leukocytosis and a high sedimentation rate that persisted during the five days from the time of entry until he was operated on. The x-ray films show the mass below and apparently in connection with or overlying the left kidney. I think I can see on one of these films the very well defined lower edge of the mass. It shows no irregularity except that it is not perfectly symmetrical. There was a question of there having been pulsation in the mass. I believe two observers thought there was. The ureter was pushed medially, the kidney was pushed outward and upward and the colon was pushed outward. I believe these findings indicate that this was a retroperitoneal mass. On the negative side there was no evidence of invasion of the

FIGURE 1.

renal parenchyma found on the x-ray examination. The calyces looked perfectly normal, but on the intravenous pyelogram they were not plainly seen. If there were a tumor of the lower pole of the kidney, one would expect it probably would either draw out the lower calyx and make it elongated and thin or blot it out entirely, but there was nothing like that to suggest an actual condition in the kidney itself. The distance from the lower calyx to the lower edge of the mass was greater than one would expect it to be if this line really represented the lower edge of a normal kidney.

The possibilities that one considers in the case of a large retroperitoneal mass are renal cyst, renal tumor, carbuncle of the kidney and a retroperitoneal tumor that is not connected with the kidney at all — one of the lymphoblastomas, perhaps. I cannot believe for a moment that this mass was a cyst. There were too many symptoms. It was

certainly not an uncomplicated cyst. I think the patient had not been ill long enough and had not had a high enough temperature for this to be a carbuncle of the kidney. The picture suggests to me a rather sudden letting loose of fluid of some type close to the kidney, within Gerota's fascia, which I believe is represented by this line. Such a fluid, if it extended over the kidney, would tend to blot out the outline of the calyces, as shown in the intravenous pyelogram. If the fluid were blood, this would account for the anemia, for the increasing white-cell count and for a greatly increased sedimentation rate.

The diagnosis, it seems to me, is not at all clear, but I do not believe that the entire picture could be accounted for by tumor, although tumor may have been a factor. I would rule out renal cyst. I think the mass was too closely connected with the kidney to be a retroperitoneal tumor of nonrenal attachment. There were not enough acute symptoms for a renal carbuncle.

I believe the picture could be explained by sudden escape of blood into the perirenal space, Gerota's fascia, which would cause an aching pain — an ache that would shift as the condition extended and would tend to disappear without anything particular being done for it as the tissues became accustomed to the increased pressure from within. I do not know the origin of the hemorrhage. It may have been a ruptured aneurysm, not a very large one, which would account for the pulsation if the pulsation had really been present. It may have come from a tumor of the lower pole of the kidney. I hope I am not saying this to cover my retreat. I have never seen a tumor bleed extrarenally to that extent. I believe the condition was caused by hemorrhage and I would think the most likely source of it was a ruptured aneurysm.

Dr. F. Dennette Adams: Did Dr. Smith consider a ruptured diverticulum?

Dr. Smith: From where?

Dr. Adams: The gut.

Dr. Smith: The barium-enema examination did not show anything. I think that if the mass were due to discharge from the bowel the x-ray films might have shown some barium within the mass. A perinephric abscess may arise from a diverticulitis.

Dr. Saul Marcus: I should like to ask Dr. Smith if he has ever seen a case of a perinephric abscess without temperature but with symptoms somewhat similar to this. I have seen two such cases that fooled me. At operation they were simply perinephritic abscesses.

Dr. Smith: Yes; I have seen that too, but I do not see how that could explain the sudden onset of ache unless there was a rupture of some false membrane. I think there would have had to be a good deal of pressure to cause the ache, and it would not clear up as quickly as it did.

Dr. Benjamin Castleman: This patient was operated on by Dr. Arthur Allen and Dr. Colby together. Perhaps Dr. Colby would tell us the preoperative diagnosis and what was found.

Dr. Fletcher H. Colby: All of us who saw this patient were unable to come to a satisfactory diagnosis. I think Dr. Smith is to be complimented for coming as near an accurate diagnosis as I believe could be made. The sudden onset of this patient's pain and symptoms was of course the outstanding feature of the whole case. It seemed to us, — and perhaps this was not brought out in the protocol as well as it might have been, — that this man had a very easily palpable large mass, as large as a grapefruit, in the left side of the abdomen. It was not very tender. The nearest we could come to a diagnosis was a retroperitoneal tumor with hemorrhage into it.

Clinical Diagnosis

Retroperitoneal tumor with hemorrhage into it.

Dr. Smith's Diagnosis

Perinephric hemorrhage, from ruptured aneurysm.

Anatomical Diagnosis

Hemorrhage into renal cyst with rupture and perirenal hematoma.

Pathological Discussion

Dr. Colby: At the time of operation, the mass was exposed through an incision in the left side and was found to be retroperitoneal. It was about as large as a grapefruit. The whole mass was movable and we thought we were dealing with a retroperitoneal malignant tumor, possibly a fibrosarcoma or a tumor of that order. However, on further dissection, the mass was freed from the large bowel and from the surrounding structures without too much difficulty. We were unable to find the kidney until almost at the end of the procedure, when it was then obvious that the mass did involve the kidney itself. The renal pedicle was clamped and the mass removed.

Dr. Castleman: In the operating room this was cut across; here in this photograph on the left is the kidney and on the right is a massive hematoma involving, as Dr. Smith predicted, Gerota's fascia (Fig. 2). The source of this hemorrhage was apparently a small cyst in the cortex of the kidney in which there was both old and fresh blood. The

capsule was elevated and there was fresh blood between it and the inner wall. A small perforation of the capsule into the surrounding fascia had produced the massive hematoma. We were unable to find any large artery, but so often in these cysts one finds only a small vessel that is close to the

FIGURE 2.

inner lining of the cyst. Another cause that one always has to think of with hemorrhage around a kidney is polyarteritis nodosa. We have seen that once or twice — a rupture of an aneurysm of an artery involved with polyarteritis producing a hematoma such as this. There was no evidence of that in any of the vessels that we examined. The patient made an uncomplicated recovery.

CASE 37462

PRESENTATION OF CASE

First admission. A forty-one-year-old man entered the hospital complaining of attacks of smelling "bad odors."

Two weeks before admission, while at work, he suddenly became aware of a peculiar odor, strong but indescribable, not especially unpleasant. This lasted but for a moment. When he tried to ask an employee about the odor, — a man well known to him, — he could not remember the man's name or the names of any of the other employees. There was no loss of consciousness, involuntary motor activity or disorientation in time or place. His memory for names returned to normal in ten minutes, and there were no other residual symptoms. For the following eight days he had similar attacks almost daily, up to three a day. In these attacks there was first a rapid succession of five or six strong odors, lasting about one to two minutes, then five to ten minutes of inability to remember people's names, even his daughter's, although there was no disorientation in time or place, no impairment of consciousness and no inability to use common objects correctly. Between attacks he was perfectly well, and the sense of smell was intact. He was free of attacks for one week before admission, except for one attack the day before entry.

All his life he had had a strong appetite for "sweets." For an unspecified period he had drunk over six pints of water daily. In the past year he had felt somewhat fatigued. Five weeks before admission he had had a single episode of severe generalized headache, accompanied by scintillating scotomas, lasting several hours, but not by nausea or vomiting. Four days before entry, he began to have daily right-frontal headaches of moderate severity, relieved by aspirin. The past history was otherwise irrelevant.

Examination revealed a well developed and well nourished man. There was no impairment of intelligence, memory or orientation and no disorder of speech. He was right-handed. There was no anosmia. The optic-disk margins were slightly blurred. The pupils, ocular movements and visual fields were normal. There were no sensory or motor abnormalities, and superficial and deep reflexes were normal. There were no other significant physical findings.

Routine examinations of blood and urine were normal. On lumbar puncture the cerebrospinal fluid was clear and colorless, under a pressure equivalent to 160 mm. of water, and contained 2 lymphocytes and a total protein of 78 mg. per 100 cc. The gold sol was 0000000000 and the Wassermann test negative. An electroencephalogram was within normal limits except for some "faintly suspicious activity" in the left postfrontal region. X-ray films of the skull and a pneumoencephalogram demonstrated normal findings. A glucose-tolerance test showed a fasting blood sugar of 82 mg. per 100 cc., a maximum rise to 139 mg. in one-half hour, a maximum fall to 67 mg. in three hours and then a rise to the fasting level in five hours. He had one seizure in the hospital, similar to the previous attacks, occurring in the midafternoon. The blood sugar at this time was 150 mg. per 100 cc. The hospital course was otherwise uneventful. In view of the findings it was thought that nothing further

could then be done, and he was sent home on anticonvulsant medication.

Second admission (six months later). At home he remained well for about three months. Three months before the second admission he had a severe attack lasting several days in which there were persistent bad tastes and smells "like burning meat and horrible dead flesh," followed by considerable mental confusion, poor memory and some difficulty in naming objects, with complete loss of memory afterwards for the period of the attack. In the first twelve hours of this attack the blood pressure was raised about 60 points systolic, and he had some "gooseflesh" of both legs, more on the left. He then had frequent attacks, up to thirty a day, beginning with "gooseflesh" in the left calf, then on the left side of the face (occasionally on the right), followed by recurrence of bad smell and taste, lasting a few minutes, without impaired consciousness or speech disturbance. Immediately before one of the attacks he saw "black devils at the window." About two weeks before readmission he had another severe attack of "smells and tastes," with some confusion. During this attack the left pupil became enlarged and poorly responsive to light; this persisted. At about this time he developed diplopia on looking upward and to the left. There were no headaches, and except for the attacks and the generalized fatigue of which he had previously complained, he remained perfectly well.

On examination there was impairment of smell in the left nostril. There was slight blurring of the disk margins. A congruous right-upper-quadrant anopia was demonstrated when the visual fields were tested. The left pupil was 2 mm. larger than the right and reacted very slightly to light and somewhat better on convergence. Extraocular movements were grossly unrestricted, but there was horizontal nystagmus on right and left lateral gaze and a slight degree of diplopia on left upward gaze, with the left image a little above and medial to the right. The motor and sensory systems were normal and the reflexes unremarkable. There was no intellectual impairment or aphasia.

Routine laboratory studies were normal. An electroencephalogram gave a normal record except for questionable abnormal activity on the left. X-ray films of the skull were not remarkable. In ventriculograms the left-temporal horn was higher than the right and was slightly compressed inferiorly. There was a questionable slight displacement of the lateral ventricles to the right.

On the twelfth hospital day an operation was performed.

Differential Diagnosis

Dr. Mandel E. Cohen*: The most impressive feature of this patient's illness was the "spells" of a rather striking nature. The "spells" included awareness of a peculiar odor; temporary inability to remember names; the occurrence of "gooseflesh" on the left calf, then on the left side of the face, and occasionally on the right; immediately before one attack the patient saw "black devils at the window"; episodes of bad smells and tastes with considerable mental confusion, poor memory, difficulty in naming and complete loss of memory afterwards for the attack; severe generalized headache accompanied by scintillating scotomas; and rise in systolic blood pressure of 60 points in one attack, along with gooseflesh. In addition to these spells, it is stated that there were a strong appetite for sweets, the drinking of over six pints of water daily and fatigue.

The above symptoms suggest that the brain was not working right, and since this was a right-handed man and speech disorder accompanied some of these spells, they suggest also that it was the left temporal lobe that was involved.

The striking symptom, that of bad odors, is characteristic of what is called an "uncinate fit"; these phenomena have been correlated with lesions near the tip of the temporal lobe, specifically the uncinate gyrus. The first description says that the odor was "not especially unpleasant." This is an unusual feature because, for some reason that is not clear, patients with uncinate fits do not smell pleasant smells. There is no known reason why these patients do not sometimes have, as an uncinate fit, an odor of Chanel No. 5, fresh flowers or some other pleasant odor, but apparently smells such as those of burning rubber, ammonia, something rotten or as in this case "like burning meat and horrible dead flesh" seem to be related to lesions near the uncinate area.

Temporary inability to remember names is not particularly localizing. However, if a patient who has had a careful language examination cannot recall names of objects but can recognize the correct

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name when it is presented to him and recognizes the nature of the object named (so-called amnesic, aphasia, or, in Nielsen's terminology, irreminiscence, auditory, verbal, temporal), this is suggestive of a temporal-lobe lesion affecting especially the posterior part of the temporal lobe around Area 37 of Brodmann, and is clinically most useful in the diagnosis of left-temporal-lobe abscesses. If the patient is temporarily found to use words badly, not to pronounce them well, not to be able to think of the right word or to mispronounce the word when it is presented to him, then it is clear that the most probable localization is the posterior part of the temporal lobe, and that lesions affecting Area 41 or 44 and their connections, that is, various "language areas," may be involved. Actually, since the aphasic phenomenon only occurred in spells, it suggests that the lesion had not actually involved Area 37 but was near it. Sometimes, in tumors, the language area involved may be at some distance from the tumor itself.

The appearance of "gooseflesh" during spells is not, at the present level of neurologic knowledge, of localizing value. On the other hand, a pathological study of such cases may throw light on the pathways and areas that are indispensable to the production of gooseflesh. (I assume here that "gooseflesh" means the appearance of tangible "goose pimples" on the skin and is not a report of the patient's having a tingling feeling of the extremities, which would have a different significance and would suggest parietal-area localization. The data do not make explicit just what the patient meant by this.) In neurophysiologic studies piloerection has been observed from stimulation of the cingular cortex in *Macaca mulata*. In some patients with hemiplegia gooseflesh may appear on the hemiplegic side, but the exact localizing value of this phenomenon is not clear. It could be said, then, that this phenomenon represents an interesting experiment of nature but is not helpful in clinical localization at the present state of our knowledge.

Seeing "black devils at the window" is also characteristic of auras of fits that occur in relation to temporal-lobe lesions. (They may also occur with occipital Area 19 lesions.) A characteristic of these is that fully-formed objects may appear; the patient may see forms — people, devils or small men. He may regard this as a moving picture, or it may seem quite real at the time. These phenomena may appear as an aura of fits with temporal-lobe lesions or may constitute the entire fit. Other phenomena, such as feelings of "familiarity," or "having experienced it before many times," or of "unreality," or of "it all being a dream," may occur in spells accompanying temporal-lobe lesions.

Confusion accompanying smells and tastes leads to the idea that these phenomena were really fits and not just irrelevant bad tastes and smells, and that the illness was progressive in extent as the spells became more severe.

The appearance of scintillating scotomas may occur either with a temporal-lobe lesion, in relation to occipital-lobe lesions, or with relation to migraine, where brain lesions have not as yet been found.

The rise in systolic blood pressure during one of the attacks brings up two questions. Was the rise a significant rise? I am not given any base-line data on which to make this deduction. If the rise was a significant one, was it related to overactivity, excessive muscular movement in a seizure, or fright or was it a "primary" manifestation of the seizures? Repeated study would be necessary to ascertain this. Even if I knew this was part of the spell, I still could not use this phenomenon, any more than I could gooseflesh, as a localizing sign, since there is suggestive evidence that blood-pressure rise may be related to stimulation of various parts of the central nervous system, particularly the orbital surface of the frontal area and the cingular gyrus and also the tip of the temporal lobe, and that it also may be secondary to phenomena provoked by disturbances of the brain or may be secondary to breathing or other muscular movements.

The symptoms that occurred in addition to the spells were a strong appetite for sweets and the drinking of over six pints of water daily. The former is of no localizing value. The imbibing of approximately 15 glasses of water daily is suggestive of the syndrome of diabetes insipidus and suggests involvement of the supraoptic nuclei, the pituitary gland or the connections between them. The fatigue suggests that the patient was ill and nothing more specific.

The symptoms add up to the suggestion that the patient had a temporal-lobe lesion and that it was most likely on the left side. Pituitary or hypothalamic involvement could result either from direct extension of the temporal-lobe lesion into

those areas or from secondary pressure; the reverse is also possible — that is, pituitary tumor may give uncinate fits as a symptom.

As the signs developed, the definite abnormalities included a large, poorly responsive pupil on the left and diplopia on looking upward, with crossed-image diplopia suggesting involvement of the third nerve due to an expanding temporal lobe; a tentorial pressure cone could also explain a large pupil. The relatively good health of the patient is somewhat against this interpretation. The left anosmia, if a new sign and if not related to rhinitis, suggests involvement of the left olfactory nerve; uncinate lesions *per se* rarely give unilateral anosmia. The quadrant hemianopia is characteristic of temporal-lobe lesions involving optic radiations.

Other disorders, such as general paresis, that do give fits of a localized nature and high protein in the spinal fluid are ruled out by the normal serology and relatively normal spinal fluid and by the displacement of the ventricular system. Vascular disease of the brain with embolism or thrombosis does not give fits as a rule and does not show a steady progression but reveals a series of abrupt clear-cut episodes.

After each point has been considered, it seems clear that the leading possibility is that of a brain tumor involving the left-temporal area. The nature and extent of this are difficult to decide from the extent of the symptoms. In a patient who is relatively well, with no metastases in the lungs and the skull, and where there is no other evidence of primary metastatic cancer, it is unlikely, after six months and careful hospital study, that the source of a metastatic neoplasm would not be discovered. A primary neoplasm of the brain is more probable.

Against the diagnosis of tumor are several findings. The spinal-fluid pressure was not elevated. A temporal-lobe tumor, however, does not of necessity give increased spinal-fluid pressure. Choked disks were not definitely noted. Again this is all right in a temporal-lobe tumor. It was reported on both occasions that the optic-disk margins were slightly blurred. So many examiners report this routinely on all optic disks as to make its significance unclear. If, however, this means that, in the opinion of the examiner, the disk margins showed abnormal blurring from which the examiner concluded that there was definite, although slight, papilledema and therefore increased intracranial pressure, this would be good evidence of cerebral neoplasm, but the statement of slight blurring is not helpful unless the descriptive norm of the examiner is known.

Further against the diagnosis of tumor is the fact that few signs have appeared, but it can be pointed out that some evidence of progression existed, as there was evidence that, in addition to the spells becoming more severe, there seemed to be ocular and olfactory involvement.

No reflex abnormalities and no Babinski sign were noted. In a tumor of this duration involving the general area of the temporal lobe one might expect at least slight hyperactivity of the deep tendon reflexes and abnormal or equivocal plantar response on the right side.

The mass would most likely have been of a slowly growing type and not extremely large. This fits a temporal-lobe astrocytoma rather than a glioblastoma, since the pressure was normal in the original lumbar puncture and because so few abnormal neurologic signs had appeared. Reticulum-cell sarcoma may occur in this region; epidermoid tumors involving the uncinate area have occurred. An angioma and a large aneurysm are also possibilities. The skull x-ray film showed, apparently, no evidence of meningioma, but this is also a possibility. The fact that the patient had no aphasia suggests that the lesion had not actively involved much of the temporal lobe, since the only aphasic phenomena appeared in fits, suggesting involvement of areas near speech areas but not of speech areas themselves.

In the absence of a source of infection, such as ears, lungs or sinuses and in the absence of a febrile course and of cells in the spinal fluid, a diagnosis of brain abscess is not a tenable one.

In a problem of this kind the laboratory data might be useful in determining the nature of the lesion. During the first admission a lumbar puncture showed normal pressure and normal cell count. The normal pressure suggests that if this was a tumor it was probably not as yet large or in a location (such as the posterior fossa) to give high pressure. The normal cell count is against the possibility of an infectious lesion. Increased protein suggests that in all likelihood this disorder was not a fixed brain abnormality such as an old scar,

a developmental abnormality or a degenerative disease but was more likely to have been a neoplasm. In neurologic diagnosis a "glucose-tolerance test" done by either routine or special technic is of no diagnostic value whatsoever in my opinion; this is not to deny its usefulness in metabolic or endocrine disorders. In cases in which the localization is not already clear or the cause of the disorder fairly obvious, I believe electroencephalographic studies rarely give useful or crucial evidence explaining the nature or localization of a lesion. In this case, a first report of "faintly suspicious activity" in the left-posterior frontal region and the second report of "questionable abnormal activity on the left" could be interpreted to mean that if this was a brain tumor or other lesion it was most likely on the left and this could be used as minor corroborative evidence.

In the second admission a ventriculogram was done. The left temporal horn was higher than the right and the lateral ventricles were displaced to the right. This further suggests a left-sided mass involving the general area of the temporal lobe.

My diagnostic impression is that this was a lesion located in the anterior part of the left temporal lobe that extended to involve the optic radiation and possibly the hypothalamus with pressure on the left third nerve and that the most likely lesion is a glioma, probably an astrocytoma.

Clinical Diagnosis

Brain tumor.

Dr. Cohen's Diagnosis

Astrocytoma of the left temporal lobe with extension to optic radiations and to hypothalamus.

Anatomical Diagnoses

Glioblastoma multiforme, left temporal lobe.
Herniation of tentorium.

Pathological Discussion

Dr. Charles S. Kubik: Dr. Cohen has made good use of the symptoms and signs and has given us an interesting and instructive discussion of the case.

The operation consisted of an exploration of the left temporal lobe. Following the operation the patient did not regain consciousness and died on the third postoperative day.

Post-mortem examination disclosed a pale, firm tumor, with poorly defined margins, approximately 5 cm. in diameter, situated, as Dr. Cohen has predicted, in the anterior inferior, medial portion of the left temporal lobe, involving the uncinate gyrus and adjacent region. The temporal lobe was enlarged medially into the notch of the tentorium, producing a pressure cone, which jammed the third nerve against the edge of the tentorium, thus accounting for the ocular signs. Although the tumor was in close relation to the optic tract a more likely explanation for the homonymous, quadrantic visual-field defect would be involvement of the optic radiation in the temporal lobe. The proximity of the tumor to speech areas and related tracts obviously accounts for the aphasic symptoms. There was little or no involvement of the hypothalamus. Although the pale color and firm texture of the tumor were suggestive of astrocytoma, microscopical examination disclosed cells that varied considerably in size and shape, many multinucleated forms and a fair number of mitoses, indicating a higher degree of malignancy, probably glioblastoma multiforme.

There were small hemorrhages in the tegmentum of the midbrain and pons, such as are frequently formed with a temporal pressure cone, which unquestionably was largely responsible for the patient's postoperative state and death. There were also a cerebellar pressure cone and pulmonary congestion and edema.

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STARK UNREALITY

NUCLEAR physicists have hypothesized to the extent of very practical applicability and acceptability that the fundamental and ultimate nature of the universe is not material and not static. The apparently most solid object is composed of a mass of moving electrical charges.

Through the ages man has wondered about the essence of reality and long since has known that nothing is actually what it appears to be from the old-fashioned, common-sense perspective. Difficult as it may be to understand or perceive immediately, a block of concrete is really a system of intangibles in rapid motion.

This conception was, no doubt, received with open arms by the Christian Scientists, substantiating as it does what they had always known in a perhaps slightly less technical way. If physical scientists in their laboratories have found that what has ignorantly been thought of as matter does not exist, it follows syllogistically that matter is illusory.

Philosophy and science, though both sometimes errant and sometimes mutually opposed, have always in heart and intent been partners in their search for truth. That they are walking more and more together in their quest is the encouraging theme of a recent most readable book by Reichenbach.* Yet these two eager, prodigious seekers are relatively immature and wholesomely deserve many of the buffets they give each other.

Medicine, supposedly, — and, it is hoped, in reality, — attracting the less primitive students, may not present a field of human endeavor in which the altercations between philosophy and science are quickly discernible. However, even here disagreements do occur. Particularly in psychiatry and its expansions there may be the makings of dissension. Psychiatry is frequently called one of the newest or youngest of the sciences. It is understandable that there is occasional wonderment concerning how the youngster qualified at all.

The efficacy of electric shock, insulin, leukotomy and antisyphilitic treatments, within stated limits, cannot be questioned. Psychotherapy of various kinds has fairly well proved its value. However, in the development termed "psychosomatic medicine" hopes and assumptions have been insinuated as facts when proof convincing to the unbiased is not present. The movement is far enough out of critical hands to permit a gullible, unknowing public to believe that it can worry itself into heart disease, hypertension and thyrotoxicosis, — in addition to peptic ulcer, — or, shortly, if divinations go on apace, into almost any disease that has previously been classified as predominantly of organic or exogenous origin. Although popular and semi-scientific journalism are inculpated, the too enthusiastic and uncritical psychosomaticists themselves are primarily responsible. Certain personality types have been concocted, reputedly prone to develop characteristic diseases. Nonsupporting or insufficient data do not impede the will to believe.

*Reichenbach, H. *The Rise of Scientific Philosophy*. 333 pp. Berkeley, California: University of California Press, 1951.

By way of an interesting, probably not easily delineable psychosocial trend, the physicists' thesis of a nonstatic universe seems to parallel or be related to the psychiatric and psychosomatic belief in the essential power and influence of the emotional or mental components in human life. It is true and well known that some of the East Indian yogis have such control over the body that they can alter autonomic functions and even dissociate pain from consciousness.

Admitting freely the importance of the mind and the psychic side of emotions, man will be, to date, sadly misled if he decides that he can successfully and healthily ignore what he has naïvely thought of as his physical structure. There are no authenticated reports of anyone's walking through a table instead of walking around it, jumping over it, crawling under it or moving the table itself to get on the other side. Up to the present, falling from a tall building to a hard surface beneath, being run over by a locomotive and being hit squarely by an automobile going at 60 miles an hour result in unmistakable alterations in the physical structure of the body, if one can at all believe his senses.

The psychosomaticist may reply, with contumely, that he makes no assertion whatever that the body cannot be injured — that his interest lies in the *cause* of injury. But undue emphasis of this interest may deter or interfere with the best treatment or may aggravate the injury. It is not exaggeration to state that some patients have been poorly treated and subjected to unnecessary expense because of the current stress on the "psycho" part of psychosomatic treatment. Considerable mental distress can be induced if a patient is made to believe that his physical illness is due to unresolved emotional conflicts or chronic emotional or personality maladjustment.

Even if some persons have a proneness to accidents, there is still a place for public safety laws in community life, and although a person may have diarrhea of emotional origin it is also possible that he may have amebic dysentery. An all-or-none principle is not compatible with the best medical discipline, and the psychosomaticist should have respect for physical factors as possibly primary, not as effect only. One should not try to walk through tables until atomic fission is complete.

YALE'S QUARTER-MILLENNIUM

Although Yale University's triumphant completion of the first quarter of its first millennium has been widely acclaimed in academic circles, — and even elsewhere, in a country conspicuously conscious of the opportunities it offers for education, — one of the best accounts of Yale's founding appeared on October 20 in the *British Medical Journal*. And small wonder, for it came from the ready pen of that most versatile of Yalemen, John F. Fulton, Sterling Professor of the History of Medicine since his retirement as Sterling Professor of Physiology at the institution in New Haven.

Yale might have been celebrating its tercentenary this year, or even earlier, instead of its quarter-millennium, had it not been for a fortuitous circumstance. John Davenport, the Oxonian who founded New Haven in 1638, had hoped also to establish a college there but found that the resources of all New England were needed "for the maintenance and advancement of Harvard College," then in the second year of its infancy. The plan was temporarily abandoned; thus did Yale, with its customary chivalry, for the first time accord the accolade to its senior friend and fondest rival.

It was therefore not until 1701, when the Cambridge college was a going concern, that ten ministers of New Haven and its environs met in nearby Branford, each wise man with his gift, appropriately, of books, and thereby through an act as it were of spontaneous generation created the living nucleus that characterizes all seats of learning — a library. In the following month a charter was granted by the General Assembly of the colony, and the first student matriculated in March, 1702.

A Harvard graduate of the Class of 1699, Jeremiah Dummer, was the next notable benefactor of the college. This young man, failing to obtain either a pulpit or a teaching appointment at his alma mater, — the two obvious ways in which an educated man could put his learning to advantage, — removed to England and there, having achieved prosperity, turned his attention to the college at New Haven, some ten years after its founding.

Dummer's contribution, like that of the ten founding fathers, consisted of books and more books,

which he collected from every possible source. More than this, he stimulated the interest of Elihu Yale, a retransplant from America, whose father had been one of the founders of New Haven. Yale contributed to the collection of books that was sent to New Haven in 1714 and shortly thereafter sent on his own account "a portrait of the King, a large box of books, and East India goods which fetched £562 12s, in the Boston market."

Overcome by such bounty, the trustees, at the 1718 commencement exercises of the college, gave to it the name of this benefactor.

Yale College, despite the fact that its medical school was not established until 1813, has nevertheless the distinction of having conferred the first medical degree in the colonies. This was granted *honoris causa*, in 1723, at the recipient's own request, backed up by a substantial gift of books, to Daniel Turner, a licentiate of the Royal College of Physicians. This degree did not, however, secure for him his desired fellowship in the Royal College.

The various episodes in the celebration of Yale's anniversary will cover the entire present academic year, coming to their close on Commencement Day, June 9, 1952.

DR. SHUCKBURGH AND THE MACARONI TOUCH

In 1755, with the French Canadians being expelled from Nova Scotia, another war between France and Great Britain was inevitable. The conflict was to last for eight years until peace was concluded by the Treaty of Paris and the whole of Canada became a British province. To fight the war, Lord Amherst called for volunteers from the British colonies in America. He established his headquarters in Rensselaer, on the east bank of the Hudson, just across from Albany, for the march north via Lake Champlain. The new men came in numbers, mostly from New England, a gay motley assemblage, the adventurous youths on horseback, singing and rollicking. Amherst was to mold them into an efficient expeditionary force, but not until a clever doctor on his staff had immortalized their spirit to the tune of "Yankee Doodle." In some way they must have reminded Dr. Richard Shuckburgh, Lord Amherst's physician, of the contemporary London dandies, the macaronis, the young men who traveled much and affected continental tastes and fashions, for when Yankee Doodle went to town he "stuck a feather in his hat and called it macaroni."

The macaronis, — or macarones, — later formed the Macaroni Club in London, but in 1758, when it is thought that Shuckburgh may have composed the verse, the term was well recognized and had become attached to certain styles of dress, such as the macaroni knot, used in tying up the hair. Even Cromwell, when he rode into Oxford on a small horse, had his single plume fastened in a sort of knot, called a macaroni. The Yankees, mostly from New England, were contemptuously referred to as "Oliver Cromwell's children" — austere, religious, but with free notions of government. One imagines the volunteer army under Amherst a little difficult to handle and rather averse to discipline and the regimentation of a soldier. It was this aspect, plus the gaiety of spirit, that attracted Shuckburgh's attention.

Of Richard Shuckburgh only a few facts are known. Born about 1705, he was on the Delaware in some capacity as early as 1735. His commission as a surgeon in the British forces was dated June 25, 1737. He resigned in 1761 but later rejoined and served in Detroit in 1765. He became Secretary of Indian Affairs in New York but died in 1773, after being in office only a few years.

That Shuckburgh was actually the author of "Yankee Doodle" is conjectural. The problem was studied thoroughly by Dr. George H. Moore of the New York Historical Society and by Albert Matthews of the Colonial Society of Massachusetts, but their researches, though thorough, left the matter in doubt, although the evidence pointed to Shuckburgh as a possible or even a probable candidate. The house used as Amherst's headquarters, where Shuckburgh is supposed to have written the verse, to a tune that was not uncommon in 1758, is still shown to visitors, and the doctor's memory is preserved in the place where he was stationed, when at least one Yankee, "with a feather in his cap," arrived in 1758, "riding on a pony."

Could not the austere universe of 1951 do with a little more "macaroni"? Long faces and gloomy prognostications now too frequently prevail. Perhaps the world needs again to hold up its head and put a feather in its cap!

THE SEEING EYE

One of the most practical uses of photography is the relatively permanent record that is made of what the camera sees. A study of this print invariably reveals details of the scene that had escaped the notice of the photographer or left no impression on his mind.

It is the attention or the visual memory of the observer that is probably at fault, however; it may be presumed that his eye takes in as much of the detail of the visual field as does the lens of the camera but that no record remains of what the eye had received.

Studies are currently in progress at the University of Wisconsin to improve visual acuity and to train the observer in an increased consciousness of what comes within the range of his vision. This "flash-training" consists in the observation of an image flashed on a screen for one tenth of a second and of drawing in the dark, on easels with large sheets of paper, what the subject had seen.

Not only has the visual acuity of students been improved by this training as much as 400 per cent, but the differences in emphasis placed on the object by different observers have been brought out. No matter how great the amount of detail that is remembered, each person sees it differently from all the others; no matter how faithful a recording instrument the eye can be trained to become, the image that it observes will be interpreted according to the emotional reactions and the past experiences of the observer.

The use of yeast in low forms of fever, dysentery, &c., has been commended several times in this Journal. It is, in its proper place, an invaluable remedy. — Western Medical Jour.

Boston M. & S. J., *November 19, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Bagnulo — Edmund G. Bagnulo, M.D., of Pittsfield, died on October 22. He was in his forty-third year.
Dr. Bagnulo received his degree from Tufts College Medical School in 1935.
His widow, three sons and two daughters survive.

Burns — Walter L. Burns, M.D., of Lynn, died on August 17. He was in his seventy-fourth year.
Dr. Burns received his degree from Harvard Medical School in 1904. He was a fellow of the American Medical Association.

Duckering — Florence W. Duckering, M.D., of St. Petersburg, Florida, died on October 25. She was in her eighty-second year.
Dr. Duckering received her degree from Tufts College Medical School in 1901.

Fiore — Autino Fiore, M.D., of Cambridge, died on October 21. He was in his thirty-fifth year.
Dr. Fiore was graduated from Tufts College Medical School in 1942.
His widow and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PRECIPITATED ANTIGENS

Since diphtheria and tetanus toxoids, with pertussis vaccine, aluminum phosphate precipitated, and diphtheria and tetanus toxoids, A. P. P., have been distributed by the Department, in ever-increasing amounts to date, the most common inquiry made to the Biologic Laboratories concerns proper administration. The proper shaking of the vial before withdrawing the dose into the syringe is the most common omission. This should be done immediately before injection. If multiple doses are taken up in one syringe, the syringe itself should be shaken immediately before *each* injection. Otherwise some doses will be too large and others too small if all are taken from the same vial.

The fall school immunization programs this year have used diphtheria and tetanus toxoids, precipitated, for the first time, in most instances.

The question has been asked many times concerning the use of this material as a "booster" in children not previously immunized against tetanus. This double antigen should be used. Although of course this certainly does not give complete protection against tetanus, it does have some value and is not wasted. For complete primary immunization against tetanus, two additional injections of tetanus toxoid must be given three to four weeks apart.

The Department recommends the following for school-age children:

One 0.5-cc. booster of double antigen (diphtheria and tetanus) given intramuscularly just prior to or after entering school; this should be repeated in five years. School children not previously immunized should receive three 0.5-cc. doses of double antigen at four- to six-week intervals.

JOHANNES IPSEN, JR., M.D.
Institute of Laboratories

NONCLINICAL NOTES

Dr. Charles C. Lund, of Boston, has been elected president of the American Cancer Society.

TESTIMONIAL TO DR. POPE

Nearly 300 friends and admirers of Dr. Alton S. Pope, director of the Division of Tuberculosis and Sanatoria of the Massachusetts Department of Public Health, met at dinner on October 18 to congratulate him on his election to the presidency of the National Tuberculosis Association.

Dr. Pope was presented with a watch, in order, no doubt, that he may control the speed with which he is going places.

CORRESPONDENCE

ANESTHESIOLOGIST WANTED

To the Editor: A full-time position as associate anesthesiologist in the Department of Medicine and Surgery will shortly be open at the Veterans Administration Hospital, West Roxbury. It is necessary that the position be filled promptly, but personal attempts to discover recruits by various members of our staff have been futile, and no applications are in the hands of the Deans' Committee.

It was proposed that an advertisement be placed in the *New England Journal of Medicine*, but a regulation on the subject was found that prohibited the use of paid advertisements of vacancies in the Veterans Administration.

The staff will be grateful for any assistance that can be given.

ERIC STONE, M.D.
Chief, Professional Services
West Roxbury, Massachusetts

MISCELLANY

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The board of directors of the Massachusetts Academy of General Practice (the Massachusetts division of the American Academy of General Practice) at its regular meeting on September 9 adopted the following resolution:

RESOLVED, That the Board of Directors of the Massachusetts Academy of General Practice favors in principle amending the Internal Revenue Code so that taxpayers not covered by a pension plan qualified under Section 165 of the Code may be encouraged by a tax credit, a tax deduction or other means to accumulate, out of current earned income, funds which would be available under appropriate regulations of the Treasury Department to provide retirement income for such taxpayers; and further

RESOLVED, That the American Medical Association Bureau of Legal Medicine and Legislation be urged to take such steps as may be necessary to draft legislative proposals to carry out the above resolution; and further

RESOLVED, That a copy of this resolution be forwarded to the American Academy of General Practice, the American Medical Association and to each Senator and Representative in Congress from Massachusetts.

BOOK REVIEWS

Therapeutic Radiology. By George W. Holmes, M.D., radiologist, Waldo County General Hospital, Maine, and Milford D. Schulz, M.D., radiologist, Massachusetts General Hospital, and instructor in radiology, Harvard Medical School. 8°, cloth, 347 pp., with 111 illustrations. Philadelphia, Pennsylvania: Lea and Febiger, 1950. $7.50.

This is a concise, practical little book (347 pages, 111 illustrations) designed particularly for medical students and for the "general practitioners of radiology." The specialist in therapeutic radiology may not find it very useful, and he may even frown on it, as it has little to say about the details of the more intricate radium treatments and not much more about supervoltage roentgen therapy. Above all, the general tone of conservatism and common sense that pervades the book would fail to appeal to the radical therapist.

The book, as defined in the preface, is for the general radiologist who must care for the majority of patients requiring irradiation. It is thoughtfully and carefully arranged, with an excellent chapter on the early history of therapeutic radiology as an introduction, followed by adequate chapters on elementary physics, biologic effects of irradiation, the planning of the course of treatment and the selection, preparation and care of patients to be treated. There are detailed chapters on the treatment of the various parts of the human body, the various types of diseases and tumors in each part and chapters on protection of the patient and personnel and on the medicolegal aspects of therapeutic radiology.

The great value of the book lies in the fact that the statements and conclusions are based on many years' actual experience in a large tumor clinic. The authors report only on their own work, which has been tried and proved valuable (and safe) in many cases. In one chapter, at least, this backfires, as the chapter on irradiation of brain tumors is weak, probably because of lack of sufficient clinical material in this field. The second great value is the conservatism inherent in the book, well explained in the preface. The third value is the constant evidence of good clinical judgment in the handling of hypothetical or actual problems concerning the various anatomic systems. Above all, the ideas are useful, practical and acceptable in everyday roentgen therapy. The authors consistently occupy the "middle ground" in therapeutic radiology — not too conservative or pessimistic and not too radical or overenthusiastic.

The book could have been improved by a more comprehensive discussion of the uses of radium, either as a separate chapter or in conjunction with the details of roentgen therapy in selected cases. More information concerning supervoltage therapy might well have been included, even though supervoltage machines are available only to a few radiologists. The doses are given as measured in air, — the common practice in this country, — although the younger radiologists are all being trained to think and speak in terms of tumor doses. A final criticism concerns the number of typographical errors, colloquialisms and involved sentences in the text, which should have been corrected in editing and proofreading.

On the whole, this reviewer recommends this book to all beginners in radiology, to medical students and to the busy community radiologist as an excellent guide for everyday problems in therapeutic radiology.

MERRILL C. SOSMAN, M.D.

The Management of the Patient with Severe Bronchial Asthma. By Maurice S. Segal, M.D., assistant professor of medicine, Tufts College Medical School, and director, Department of Inhalational Therapy, Boston City Hospital, Boston. 8°, cloth, 158 pp., with 16 illustrations and 7 tables. Springfield, Illinois: Charles C Thomas, 1950. (Publication Number 76.)

In this 158-page monograph Dr. Segal has given us a timely review of the theoretical background and the practical application of the management of one of the most difficult diseases to handle. Not only is the subject treated in a well organized manner, but the author keeps before us the patient's viewpoint, a matter of no little importance to one who is afflicted with this dreary disorder.

The chapters on protection studies and on the use of various therapeutic gases, including aerosis, are of particular interest, as they are based on the author's wide experience in these fields. The book contains many sound, practical suggestions

for treatment. Not all of these will, of course, meet with universal approval, such as the statement that "the use of the hypodermic needle for self medication (of epinephrine) should be avoided" on the grounds that these patients become dependent on this crutch and may often become adrenalin-fast and that they frequently present altered personalities. These developments may possibly come to pass. Many allergists, including the reviewer, however, believe that the "educated" severe asthmatic should become familiar with his epinephrine syringe and needle and should be able to handle these as successfully as the diabetic patient his insulin equipment. To accomplish this end, the physician must take great pains to educate his patient in the indications for and the dangers of this form of medication and must supervise its use at all times.

The author's other words of caution in regard to the handling of the epinephrine-fast patient are pertinent, and the chapters on sedation and the management of infection are sound.

Dr. Segal's excellent treatise will give the general practitioner, the internist and the allergist additional armament with which to understand and treat the severe asthmatic.

WALTER S. BURRAGE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Dimensional Analysis for Students of Medicine. By Harold A. Abramson, M.D., assistant clinical professor of physiology, Columbia University, associate physician and chief, Allergy Clinic, The Mount Sinai Hospital, New York City, and consultant (psychology), Department of the Army. 8°, cloth, 41 pp. New York: The Josiah Macy, Jr., Foundation, 1950. $1.00 (special prices for quantities).

This manual of analysis is mathematical in concept and deals with chemical, physical and electrical formulation. There is a chapter on the circulatory system. The preliminary chapter is devoted to a general discussion of a simple technic for mathematical equations to be used in teaching the preclinical and clinical sciences.

Somatic and Psychiatric Treatment of Asthma. Edited by Harold A. Abramson, M.D., associate physician and chief, allergy clinic, The Mount Sinai Hospital, New York, and assistant professor of physiology, Columbia University College of Physicians and Surgeons. 8°, cloth, 751 pp., with 18 tables. Baltimore: The Williams and Wilkins Company, 1951. $11.00.

The purpose of this composite book is to co-ordinate the present knowledge of the allergic nature of asthma with certain methods of treatment connected with psychogenic aspects of the disease. The work is the joint effort of thirty-four specialists in their particular fields. The preliminary chapters deal with basic concepts, general testing and treatment and the nature of inhalant allergens and their treatment. These are followed by sections on somatic therapy and psychotherapy. There is a special chapter on asthma in Cuba and other Latin American countries. Lists of references are appended to the various chapters, and there is a good index. This comprehensive monograph should be in all medical libraries and available to all physicians interested in this problem.

Handbook of Diagnosis and Treatment of Venereal Diseases. By A. E. W. McLachlan, M.B., Ch.B. (Edin.), D.P.H., F.R.S. (Edin.), consultant in venereal diseases, Bristol Clinical Area, and lecturer in venereal diseases, University of Bristol. Fourth edition. 12°, cloth, 368 pp., with 160 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $4.50.

This new edition of a standard manual has been revised to include the use of penicillin in the treatment of syphilis and gonorrhea. The printing was done in Great Britain.

Methods of Vitamin Assay. Prepared and edited by the Association of Vitamin Chemists, Incorporated. Second edition, revised and supplemented. 8°, cloth, 301 pp. New York: Interscience Publishers, Incorporated, 1951. $5.50.

This standard reference book has been revised to bring the subject matter up to date. Material on members of the vitamin-B complex, not included in the first edition, is contained in this edition, namely, discussions of pantothenic acid, pyridoxine, folic acid, biotin, vitamin B_{12} and niacin. The chapter on "methods for other vitamins" has been extended to make it more valuable for investigators. Extensive lists of references are appended to the various chapters. The material is well arranged and the book is well published. It should be in all collections on the vitamins.

Patterns of Sexual Behavior. By Clellan S. Ford, Ph.D., associate professor of anthropology, Yale University, and Frank A. Beach, Ph.D., professor of psychology, Yale University. With a foreword by Robert Latou Dickinson, M.D. 8°, cloth, 307 pp., with 16 illustrations. New York: Harper and Brothers, 1951. $4.50.

The findings in this study of sexual behavior are based on a detailed analysis and comparison of the sexual patterns of one hundred and ninety contemporary societies. They were carefully selected to provide a representative cross-section of varying human cultures, ranging from the Arctic to Australia, and from the most isolated primitives to modern society. The courtship and mating of a considerable number of animal species were also studied. The authors state that a comparison of the behavior of human beings and animals indicates that certain types of sexual activity arise from biologic factors rather than from social customs and pressures. Concerning homosexuality, it was found to exist in nearly all the societies studied and also among a number of species of animals. The authors therefore suggest that "human homosexual tendencies have a definite biological basis" and "appear to exist in a large majority of both sexes, although they may never be recognized and although no overt homosexual behavior may occur." "Finally, a study of the physiology of sex, in both humans and animals, indicates how sexual behavior is molded by such factors as blood chemistry and development of the brain." There are an extensive glossary of terms, a bibliography and indexes of authors and subjects. The material is well arranged and the text well written. The publishing is excellent. The book should be in all scientific collections on the subject.

Textbook of Physiology and Biochemistry. By George H. Bell, B.Sc., M.D. (Glasg.), F.R.F.P.S.G., F.R.S.E., professor of physiology in the University of St. Andrews at University College, Dundee; J. Norman Davidson, M.D., D.Sc. (Edin.), F.R.F.P.S.G., F.R.I.E., F.R.S.E., Gardiner Professor of Physiological Chemistry, University of Glasgow; and Harold Scarborough, M.B., Ph.D. (Edin.), F.R.C.P.E., professor of medicine in the Welsh National School of Medicine, University of Wales, and director of the medical unit in the Royal Infirmary, Cardiff. With a foreword by Robert C. Garry, M.B., D.Sc. (Glasg.), F.R.F.P.S.G., F.R.S.E., Regius Professor of Physiology, University of Glasgow. 8°, cloth, 918 pp., with 55 illustrations. Baltimore: The Williams and Wilkins Company, 1950. $9.00.

This new textbook on the combined subjects of physiology and biochemistry is intended as an introduction for medical and other interested students. The authors are three well known British physicians who, in their treatment, consider the two subjects as one, because of their intimate relation, and wherever possible indicate their relevance to clinical problems. The material is well arranged and well written. For students who desire to follow any subject further, lists of selected references are appended to the various chapters. The close interrelation of the two subjects is emphasized by the numerous cross-references in the text. There is a comprehensive index and the publishing is excellent. The book should be in all collections on these subjects.

A Handbook on Diseases of Children (including dietetics and the common fevers). By Bruce Williamson, M.D. (Edin.), F.R.C.P. Lond., physician, Children's Department, Royal Northern Hospital, London, Prince of Wales General Hospital, London, Wellhouse Hospital, Barnet, Enfield War

Memorial Hospital, and Hornsey Central Hospital, London, examiner in medicine, General Nursing Council, and consulting physician, Pioneer Health Centre, Peckham. 12°, cloth, 440 pp., with 94 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $4.50.

The first edition of this British handbook was published in 1933. This sixth edition has been thoroughly revised to bring it up to date. The original format has been retained. There is a good index and the book is well published. The printing was done in Great Britain.

An Introduction to Universal Serologic Reaction in Health and Disease. By Reuben L. Kahn, D.Sc., University of Michigan Medical School and Hospital, Ann Arbor, Michigan. 12°, cloth, 155 pp., with 113 charts. New York: The Commonwealth Fund, 1951. $3.50.

In this special monograph Dr. Kahn presents experimental data indicating that serologic reactions with lipid antigen, elicited by an appropriate technic, are widely applicable in health and disease. The preliminary chapters discuss the technic of universal serologic reactions and their patterns in normal human beings and animals. The succeeding chapters deal with syphilis, yaws, leprosy, malaria and tuberculosis. These are followed by special chapters on studies of institutionalized children, technical studies and the nature and significance of the reaction. There are 113 special charts. The book is well published, in the typical Commonwealth Fund style, and should be in all collections on the subject.

The Student's Handbook of Surgical Operations. By Sir Frederick Treves, Bart., G.C.V.O., C.B., LL.D., F.R.C.S. Ninth edition, revised by Sir Cecil Wakeley, K.B.E., C.B., D.Sc., P.R.C.S., F.R.S.E., fellow of King's College, London, senior surgeon to King's College Hospital, director of surgical studies and teacher of operative surgery, King's College Hospital Medical School, surgeon to the Royal Masonic Hospital and Belgrave Hospital for Children, consulting surgeon to the Royal Navy, Hunterian Professor, Royal College of Surgeons of England, and examiner in surgery, University of Cambridge. 12°, cloth, 580 pp., with 269 illustrations. New York: Paul B. Hoeber, Incorporated, 1951. $5.50.

Sir Frederick Treves first issued his popular handbook in 1892. The text of the 1947 edition has been revised to include new operations on the heart, lungs, brain and spinal cord. The text has been thoroughly revised and brought up to date, and many new illustrations have been added and old ones deleted. The printing was done in Great Britain.

Arzt und Laboratorium: Die chemischen und mikroskopischen Untersuchungsmethoden und ihre Verwertung am Krankenbett. By Hellmut Marx, M.D. Seventh edition. 8°, paper, 192 pp., with 18 illustrations and 5 tables. Stuttgart: Georg Thieme, 1951. DM 8.70. Distributed by Grune and Stratton, Incorporated, New York.

This laboratory manual was first published in 1939. The seventh edition has been revised and brought up to date by Dr. O. H. Arnold. There is a good index of subjects, and the publishing is well done.

Die Frühdiagnose des Uteruscarcinoms: Unter besonderer Berücksichtigung des Schridenabstrich Verfahrens nach Papanicolaou. By Hans Limburg, M.D., Universitäts-Frauenklinik, Hamburg. 8°, paper, 158 pp., with 75 illustrations and 16 tables. Stuttgart: Georg Thieme, 1950. DM 14. 8°. Distributed by Grune and Stratton, Incorporated, New York.

This new monograph on the Papanicolaou procedure is a comprehensive review of the subject to date. There is an extensive bibliography. The publishing is excellent; the monograph should be in all collections on cancer and gynecology.

Pioneer Doctor. By Lewis J. Moorman, M.D. 8°, cloth, 252 pp., with 12 illustrations. Norman: University of Oklahoma Press, 1951.

Dr. Moorman was a real pioneer doctor who, born in 1875 and brought up on a farm in Kentucky, went to Oklahoma after graduation from medical school. Settling in Jet, twenty miles from the nearest railroad station, he was busy in the fertile farmland of wheat and alfalfa. After six years there he went to Oklahoma City, where he developed an interest in tuberculosis, founded a dispensary and later became editor of the *Journal of the Oklahoma State Medical Association.* The last half of the book deals largely with tuberculosis, with a splendid review of the history of the disease. This autobiography is written in a philosophical vein. The style is diffuse and discursive, but there is much of interest for the persistent reader.

NOTICES

ANNOUNCEMENT

Dr. Helen S. Pittman announces that Dr. Rita M. Kelley has become associated with her in the practice of internal medicine at 264 Beacon Street, Boston.

SOUTH END MEDICAL CLUB

The next luncheon-meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 20, 1951, at noon. The speaker will be Dr. Richard Ford, Medical Examiner, Suffolk County, Southern District, assistant professor and acting head, Department of Legal Medicine, Harvard Medical School, and expert assistant in pathology to the Massachusetts Department of Public Safety. His subject will be "Medicolegal Investigation of Sudden Death." Physicians are cordially invited to attend.

BOSTON SOCIETY OF BIOLOGISTS

The Boston Society of Biologists will present a symposium on steroid compounds in the amphitheatre of the Peter Bent Brigham Hospital on Tuesday, November 20, at 8 p.m. Dr. George W. Thorn will preside.

Dr. Louis F. Fieser will speak on "A Natural Isomer of Cholesterol," Dr. Lewis L. Engel on "Recent Studies on Estrogen Metabolism" and Dr. Gregory Pincus on "Adrenal Steroid Metabolism."

All interested physicians are invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The New England Society of Physical Medicine will hold a meeting on November 21, at 8:00 p.m., at the Hotel Kenmore, Boston. The program will feature reports and discussions by members and guests concerning "Advances in Physical Medicine During the Past Year."

Physicians, physical and occupational therapists, nurses and medical students are invited to attend.

MASSACHUSETTS SOCIETY FOR RESEARCH IN PSYCHIATRY

The schedule of meetings of the Massachusetts Society for Research in Psychiatry for the coming year is as follows:

Monday, January 7, 1952 — Ring Sanatorium, Arlington;
Monday, February 25 — Cushing Hospital, Framingham; and Tuesday, April 15 — Boston Psychopathic Hospital, Boston.

COMMONWEALTH AND EMPIRE HEALTH AND TUBERCULOSIS CONFERENCE

The third Commonwealth and Empire Health and Tuberculosis Conference will be held in London, England, in July, 1952, under the sponsorship of the British National Association for the Prevention of Tuberculosis. Lectures and discussions concerning vaccination, treatment, bovine tuberculosis infection, chest clinics, social workers' problems and the prevention and control of tuberculosis will be held July 8-11. Visits to sanatoriums, hospitals and clinics will take place July 11, 12 and 13.

Further information may be obtained from the Secretary-General, National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W. C. 1, England.

(*Notices concluded on page xv*)